PRINCIPLES OF DIAGNOSIS AND TREATMENT IN HEART AFFECTIONS

OXFORD MEDICAL PUBLICATIONS

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THIRD EDITION

LONDON
HENRY FROWDE AND HODDER & STOUGHTON
THE *LANCET* BUILDING
1 BEDFORD STREET, STRAND, W.C. 2
1927

First Edition - 1916
Second Impression 1916
Third " 1917
Fourth " 1918
Second Edition - 1923
Second Impression 1924
Third Edition - 1926
Second Impression 1927

PRINTED IN GREAT BRITAIN RICHARD CLAY & SONS, LTD., PRINTERS, BUNGAY

PREFACE TO THE THIRD EDITION

The most characteristic feature of Sir James Mackenzie's later teaching is its insistence upon the necessity of a proper study of function.

The gradual development of this conception can be traced throughout the whole of his earlier work, but it is only in his later writings that it attains its full expression.

As the result of certain researches into the nature of disease processes, carried out at the St. Andrews Institute for Clinical Research during the five years of his Directorship, there was evolved what is now known as the principle of the reflex arc. This principle is based upon the view that the great majority of *symptoms* owe their origin to variations in the *functional* activity of organs; and has for its object the determination of the nature of the particular functional disturbance present, and the location, in the regulating mechanism of the organ, of the point at which the disturbance in question is manifested.

This involves an entirely new conception of medicine, not only in regard to the manifestations of ill-health, but also in regard to the nature of the normal functioning of the various organs of the body.

In preparing the present edition, the main object has been to make it representative of the newer teaching of its late author, without sacrificing, in any way, the distinctively clinical character of the original work.

This has necessitated a considerable amount of condensation, but it is hoped that nothing essential has been omitted.

For a full exposition of the principles summarised and illustrated in this book, the reader is referred to the fourth edition of Sir James Mackenzie's *Diseases of the Heart*, and to his *Basis of Vital Activity*.

J. O.

The James Mackenzie Institute for Clinical Research,
St. Andrews.
July 1926.

PREFACE TO THE SECOND EDITION

The purpose of this book was to present the recent advances of cardiology in a form that would be understood by the general practitioner, and if possible, to describe the more important phenomena in such a way that they could be recognised by the trained senses of the observer. Such an endeavour was not easy to accomplish, nor can it be said that it was entirely successful; nevertheless, it has helped a great many general practitioners, as the demand for the book has necessitated repeated reprints.

In presenting a second edition I felt that as I had been so long out of touch with general practice, it would be better that it should be edited by one actively engaged in general practice, so I asked Dr. James Orr to undertake this task.

J. M.

PREFACE TO THE FIRST EDITION

The contents of this book were prepared as lectures to be delivered to the post-graduate students and workers at the Cardiac Department of the London Hospital. The outbreak of the war prevented their delivery, and in publishing them I divide the matter into chapters instead of lectures, while I retain the colloquial form of expression.

A great deal of our recent knowledge of heart conditions has been attained by the use of such mechanical aids as the polygraph and the electrocardiograph. These instruments are not available to the general practitioner, so that if the recognition of diseased conditions were to depend on their use, much of our recently acquired knowledge would be of little practical value. It has been a constant endeavour on my part to recognise the different conditions which these instruments have revealed by employing the ordinary bedside methods of examination, and I am concerned mainly with them in this book. Those who wish for the evidences which the mechanical aids have produced are referred to my book on Diseases of the Heart.

As the main question in every examination of the heart is concerned with heart failure—whether it is present or foreshadowed—one of the objects I have in publishing this book is to present the essential matters connected with heart failure in such a manner that the general practitioner can appreciate them and apply them in his practice.

Another object I have in view is to present this subject in such a form as to lead to a better conception of what clinical medicine means and how clinical investigations should be carried out, and, if possible, to stimulate research on lines which are essential to advance, but which have been wholly neglected.

I have to thank my friends Dr. George A. Sutherland and Dr. R. M. Wilson for their kind assistance and suggestions.

J. M.

PART ONE

CHAPTER I

General Remarks on Viruses, Viral Infections and Associated Cardiovascular Involvement

A GREAT NUMBER of infections are caused by viruses. In many cases, especially in viral exanthematous diseases, the clinical features are so characteristic that diagnosis can be made without laboratory investigation. In others, the viral causal agent can be identified by isolation of the virus and/or demonstration of specific antibodies of the patient. Some infections are probably produced by viruses which have not yet been determined. For example, in benign inoculation lymphoreticulosis (cat-scratch disease), culture has not been successfully carried out and though there is not always cross immunity to other members of the psittacosis-lymphopathia-venereum group of viruses, it is highly probable that the causal agent belongs to this group which included in 1939 only four members but has in the meantime grown considerably.

New viruses have been discovered but our understanding of their exact part in human disease falls behind the knowledge of their physical and biological properties as demonstrated in the laboratory. One of the most interesting contributions to the progress of knowledge in virology is the discovery of the family of Coxsackie viruses. These viruses are able to produce herpangina, the frequent disease of childhood, and another non-fatal illness, epidemic (and endemic) pleurodynia.

The exact nature of viruses is not known. The question, often raised, as to whether they are alive or not, is idle and can be answered both ways. Essential is the knowledge that alternative changes of static and dynamic phases characterize the aspect of viruses (Weidel). This may explain the ambiguity of the term "life of virus." The fact that some viruses are relatively simple nucleo-proteins offers no adequate foundation to decide that they are lifeless matters having no selfsubsistent being. Burnet stresses the fact that viruses reproduce by replicating their structure at the expense of suitable atomic groups within the living substance of a susceptible cell. No alternative description of the replication has been able to replace the view that it is a simple example of biological reproduction.

Viruses are obligate intracellular parasites. The living cell invaded by virus is characterized by a high activity which is a necessity to produce new generations of virus. Virus particles are melted together with the functional mechanism of the cell harboring it. It has been said that the viruses are degenerated building blocks of the host cell because the viruses capture the machinery of living cells they invade, and it is this machinery that produces a new generation of viruses. If we recognize that certain substances of the living cells offer the conditions for the synthesis of new virus we should pay attention to the fact that new duplicates of virus can only be produced within the cell in the presence of the *viral* ribonucleic acid. By using radioactive tracers to label the essential gene component, investigators could follow the progress of *viral* deoxyribonucleic acid from parent to offspring.

The host organism is damaged by the viral attack on certain cells and tissues. The sequelae of the virus invasion depend on the change of viral particles to a complete viral agent capable of replication and on intracellular alterations of the host cells. The host cell is gradually exhausted; first, there is an increase in nucleic acids but later major cytologic alterations develop. According to Burnet, the intensity of symptoms in viral infections is probably best considered as essentially a measure of cell damage that is occurring, the symptom-producing agents being soluble products of the break-down cell. The more sudden the liberation of such products, the more acute the synptoms.

Symptoms in viral infections are also dependent on capillary damage which leads to increased permeability, protein leakage into the tissue and their sequelae.

The specific pathology of viral diseases is confined to specific cell groups, but the frequent importance of more or less simultaneous vascular damage cannot be denied.

An absolutely satisfying classification of viral diseases does not exist Viruses have an undeniable but not always perfect affinity for certain cells or tissues of the host.

They are called dermotropic, neurotropic, meningotropic, pneumotropic, viscerotropic, cardiotropic. Some viruses have a preference for several tissues simultaneously. Others may be even pantropic. There may be a different response of animals to experiments with the same virus. The suckling mouse may be more susceptible to certain infections than older ones. Interesting changes in tissue tropism under experimental con-

ditions have been reported for many viruses. Viruses are liable to alter their properties on continued passages. Well known is the gain of neurotropism and the loss of viscerotropism resulting from intracerebral passages of the yellow fever virus. There is a loss of neurotropism and gain of dermotropism when Western equine encephalomyelitis virus is transmitted serially in the pads of guinea pigs. The classification of human viral diseases according to the predominant clinico-pathologic features of the infection and the organs or tissues affected is consistent with practical needs. In the future study of detailed structure of viruses by the electron microscope and of their serologic properties (i e. their different antigenic structure) may lead to a more acceptable classification of viral diseases.

The discovery that some viruses are absorbed to and agglutinate erythrocytes of a wide variety of species became a help in identification of viral agents and has facilitated virus research. The clumping of red blood cells by viruses is specifically inhibited by homologous immune sera. This leads to the practical use of agglutination inhibition tests and may establish even a retrospective diagnosis of some virus infections.

Viruses grow in the cells of fertile hen eggs provided they are incubated for varying lengths of time

In some viral diseases there is a lasting immunity but others have only a short and type-specific immunity. The development of infection immunity depends on virus living in the body. Occasionally there is a flare-up and outward spread in a virus infection as in herpes simplex following the action of some stimuli. The mechanism by which infection in viral diseases is relinquished and subsequent resistance sustained may be based on the production of specific antibodies Neutralizing antibodies have attained great significance for the diagnosis of viral diseases. Apart from neutralization tests specific complement fixation plays a role in studying viral infections Secondary bacterial infections occur simultaneously with some viral infections.

The primary bodily effects of virus invasion are proliferation and/or degeneration of cells Inflammatory alterations are secondary to destruction of cells representing a reaction of the tissues of the host In the stage of incubation, it is already decided whether the infection sticks, i.e. whether the preconditions are given for a generalized reaction of the host on the viral invasion (Hoering)

In the incubation period, there may already be a primary short viremia. In the second stage, the period of generalization (the "vascular" stage),

viruses are present not only intracellularly but spread extracellularly through the bloodstream into the body; as a consequence of this viremia inclusion bodies and virus aggregates may sometimes be found within the endothelial cells lining the vessels of organs in some viral infections evidenced by a positive Feulgen test. The following stage of organ manifestation offers the characteristic clinicopathologic picture of illness. Many alterations of the cardiovascular system occur during the course of viral diseases. The reaction of organs to any irritating agent is rather uniform, the pathohistologic picture of the cardiovascular involvement in various viral diseases is similar.

Myocardial involvement during viral diseases may be brought about

(1) by direct action of the viral agent. There may also be present

(a) superinfection or interference (suppression of one viral infection by another). (Interference in man and animals has been demonstrated between different viruses or between strains of a single virus. The first virus in the tissues interferes with the growth of the second *An example of interference of unrelated viruses in animals is that the occurrence of the strongly interfering cardiotropic virus Columbia SK or MM excludes the virus of poliomyelitis.*)

or (b) provocation (Bieling) (concurrence of two viral infections may produce enhancement of one by another). (A virus which is latent in the body may be activated by a stimulus, i e by a new infection. Viruses which exist in a latent form within the body waiting to be activated to cause symptoms are the encephalomyocarditis [parapoliomyelitis] virus and that of herpes simplex [Bieling].)

(2) by secondary bacterial infections

(3) by antigen-antibody reaction in the heart.

(Infectious mononucleosis without heart involvement may subsequently show a scarlatiniform rash and, later, an allergic myocarditis.)

In many viral diseases capillary damage with its sequelae (i e. increased capillary permeability, protein leakage into the tissues of many organs, hemodynamic deficiencies) should be carefully considered in the search for the explanation of clinical features.

Rickettsias, though not classified as viruses, are usually considered along with them. The rickettsias are responsible for severe and mild diseases; they occupy a biologic position between bacteria and viruses, being

considered like bacteria in morphology and resembling viruses as obligate parasites incapable of multiplication apart from living cells.

According to Ash there is much similarity in the pathology of the various rickettsial diseases. The changes are diffuse rather than localized. In severe rickettsial diseases the vascular system is primarily affected and the first localization of the rickettsiae is the endothelium of the capillaries. The rickettsiae invade the circulating tree, causing swelling of the endothelial cells with thrombosis of smaller and occasionally of larger vessels. Focal vasculitis and perivasculitis may develop with foci of resulting necrosis in adjacent tissues especially in the heart, brain, kidneys and muscles. A variable degree of acute myocarditis of focal or diffuse distribution may be present and occurs to some extent in many cases, but not much evidence of degeneration of myocardial fibres is observed. Phenomena of circulatory failure are predominantly of peripheral origin.

The incubation period in severe rickettsial diseases ranges between seven and twenty days. The stage of generalization follows the incubation period. During this stage there is rickettsemia. A true organ-manifestation does not exist. Rash, cerebral and cardiovascular involvement already develop during the period of generalization and may slowly disappear after that stage. In Brill's disease, a recrudescence of a previous typhus fever, cardiovascular involvement is sometimes demonstrable by hypotension and by the electrocardiogram. A cardial form of Brill's disease has been reported. Certain intracellular parasites (viruses and rickettsias) may continue to parasitize a host for many years after the initial invasion, e.g. herpes simplex. Brill's disease and trench fever are models for the survival of rickettsias, for in these, a new attack may occur after a long period of time.

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CHAPTER II

Present Cardiovascular Concepts of Virus Diseases

DOBRINO recently pointed out that in virology facts of biological investigations occupy an ever increasing space. At the same time morphology seems to have lost a great deal of usefulness in studying viral infections. Serologic methods and biological tests are producing a rapid growth of knowledge especially in etiologic problems of viral maladies. But for the sake of our patients we have to deal mainly with clinical medicine and pathology. The struggle of the infectious agent with the host-organism, the conditions upon which depends getting ill, the symptoms, the course and the complications of the disease require studies which are best acquired from pathology and clinical medicine.

Systematic investigations of cardiovascular involvement in viral diseases have already brought much information, but the abundance of new queries is a sign for the needs in this field.

Important changes in cardiovascular concepts of viral diseases have occurred, especially in recent years. This has been achieved in three directions and in three phases. The first phase has been characterized by systematic histologic examination of the heart in fatal virus infections. The main feature of the second phase was electrocardiographic studies during the course of the disease. The last stage consisted of biochemical investigations together with a circulatory-physiologic approach to cardiovascular problems. The sequential physiologic derangements in many virus diseases must be analyzed in the future. A synthesis of the results, thus obtained by manifold studies, makes it possible to form a better idea of what is occurring in viral diseases.

For a sound understanding of the cardiovascular problems the physical examination of the patient, especially examination of the heart and blood vessels, inspection, palpation, percussion, auscultation, sphygmomanometry, electrocardiography and sometimes radioscopy are essential. Apart from the usual blood examination, chemical analysis of the blood and urine are important for diagnosis, prognosis and therapy Those interested in hemodynamics have ample opportunity to study hemodynamic changes in viral diseases.

Occasional reports on myocardial disease in some viral infection appeared before the year 1942. Heart involvement was reported in influenza, yellow fever, smallpox, encephalitis, psittacosis, poliomyelitis, mumps and measles. Since 1942 many pathologists have started analyzing systematically the morphologic changes of the heart observed in fatal cases of viral diseases. According to Ungar, several generations of pathologists have been trained to take blocks of the myocardium routinely through the central portion of the wall of the left ventricle for histologic sections. The chances for observations of lesions are lower in the "traditional" block of tissue than in certain other areas of the heart, in myocarditis only limited portions of the myocardium may be attacked (Saphir, Ungar, Wuhrmann).

The following chief histologic features of cardiac involvement in viral diseases are reported:

1) interstitial inflammation
   a) with cell infiltration
   b) with interstitial edema
2) damage of myocardial fibres
   a) albuminoid or fatty metamorphosis
   b) focal necrosis, vacuolization, fragmentation of muscle fibres
   c) hemorrhages into cardiac structures

In poliomyelitis, the picture is one of interstitial myocarditis and/or focal necrosis, vacuolization and fragmentation of myocardial fibres and, in most cases, interstitial edema The heart was found to be severely affected in approximately 30 per cent of fatal cases (Jungeblut and Edwards). In necropsy material from seventy patients with bulbar poliomyelitis Fox, Sennett and Kuzma found an interstitial inflammatory reaction in about half of their cases According to Teloh, the incidence of myocarditis during an epidemic in 1949 was much greater than in any other year (100 per cent), and also more severe. This corroborates evidence of the presence, during certain epidemics, of viscerotropic strains of the virus which may injure the myocardium Experimental work has shown that carditis in human poliomyelitis is caused by direct action of the virus on the heart (Jungeblut and Edwards)

In some experimental and human viral encephalitides, cardiovascular involvement has been observed The coincidence of "parapoliomyelitis" with myocarditis has been described Interstitial myocarditis was reported in influenza A infection, primary atypical pneumonia, psittacosis, infectious mononucleosis, acute epidemic encephalitis, viral hepatitis, and varicella. It has been maintained that mumps may produce heart damage

consisting of an interstitial myocarditis characterized by a fibrinous exudate. Coxsackie viruses may produce inflammatory change with infiltration of mononuclears and some polymorphonuclears in the myocardium of suckling mice depending on the strain. In epidemic hemorrhagic fever, a disease probably of viral or rickettsial origin, the heart shows subendocardial hemorrhages confined to the right auricle but there may also be interstitial myocarditis.

Degenerative involvement of the heart muscle fibres was described in smallpox but there the changes are sometimes of an inflammatory nature. Fatty degeneration of the myocardial fibres in yellow fever may be striking, even to the extent that it may be grossly evident in the flabby condition of the organ, but there is little, if any, interstitial reaction (Ash, Bugher, Cannell).

Severe myocardial involvement in yellow fever, in poliomyelitis and other virus diseases may already develop in the early stages of these illnesses.

The myocarditis encountered in viral infections need not always be caused by the respiratory virus or by the virus alone. Bacterial infections may complicate severe cases and make a primary viral myocarditis more severe or may be the only cause of myocarditis, endocarditis or pericarditis.

If the oxygen supply to the heart is decreased, viral heart disease may be aggravated. A pneumonia or respiratory distress may intensify an existing myocarditis by secondary (bacterial) infection and/or by hypoxia. Weinstein and Shelokov maintain that in poliomyelitis the mild form of myocarditis is hypoxic in origin whereas the severe form may be due to a direct viral invasion of the heart Georg, Halden and Vimtrup are of the opinion that, although a specific myocarditis may perhaps occur in poliomyelitis, the majority of the pathological and electrocardiographic changes described in this disease should be explained "as results of anoxia and altered pulmonary circulation." Pearce and Lange are of the opinion that anoxia is the determining factor in the occurrence of experimental virus myocarditis. Pearce thinks that the lodging and multiplying of virus in the heart are greatly facilitated and the severity of the damage there is enhanced if the oxygen supplied to that organ is drastically reduced in the initial period of infection. The significance of anoxia in the development of myocarditis also appears from experimental CO-poisoning but this "myocarditis" does not assume the proportions it does in Pearce's

experiments. It may also be questioned whether myocarditis in poliomyelitis with respiratory difficulties is merely the result of hypoxia. In *fourteen* cases of myocarditis out of a total of thirty-five cases of fatal poliomyelitis observed by Ludden and Edwards, there was no specific correlation of the type of paralysis—bulbar or spinal—with the presence or absence of myocarditis. Three of the six patients who died suddenly, showed myocarditis and had bulbar involvement which might have explained these sudden deaths. According to Fox, Sennett and Kuzma, patients without bulbar involvement (and therefore with nothing to produce anoxia) may have myocarditis while conditions known to produce chronic hypoxia, such as advanced pulmonary disease, are not ordinarily associated with myocarditis. Hypoxia and a reduced concentration of labile tissue oxidase in some myocardial parts may, however, play a role in intensifying the heart disease in virus infections (Lyon 1950). According to Fox, Sennett and Kuzma, it is conceivable that the three strains of poliomyelitis virus, already recognized, may be cardiotropic in different degrees. To confirm or refute this explanation it would be necessary to ascertain the prevalence of myocarditis in different outbreaks caused by different strains of virus.

In many cases of viral diseases cardiac damage remains the immediate cause of death; in other cases interstitial myocarditis is minimal, and the damage to the myocardial fibres relatively small.

Sterile, verrucose endocarditis occurs in poliomyelitis (Ludden and Edwards, Luhan, Weinstein and Shelokov) and has been found in some other viral diseases.

There were instances of pericarditis in viral diseases (measles, smallpox, infectious mononucleosis, psittacosis, poliomyelitis, virus pneumonia, lymphogranuloma venereum) It is not always possible to tell whether the changes are attributable to the causative virus infection. Several possibilities concerning the pathogenesis of pericarditis are to be considered. The first is the proximity of the hilar lymph nodes with the extension of the infection into the pericardial sac; another is a virus infection of the pericardium; the third possibility is a response of the pericardium as a shock organ to an offending allergy in a sensitive person (Miller, Urrichio and Phillips). In viral diseases long lasting recurrent fever, cyanosis, respiratory embarrassment, dilation of the heart, bradycardia, tachycardia and arrhythmias are indicative of severe myocarditis but the absence of clinical symptoms does not preclude severe involvement of the heart.

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it is necessary to be acquainted with the clinical condition of the patients and to know whether drugs which may change the electrocardiogram have been taken. Abnormal tracings in viral diseases also occur in the absence of demonstrable heart diseases. An abnormal electrocardiogram observed during an acute condition, even in patients with heart diseases, does not necessarily establish a causal relationship between the acute disease and the electrocardiographic abnormalities which may have been present before. Caution is indicated in interpreting electrocardiographic findings; they should always be checked against clinical evidence.

Electrocardiographic diagnosis in viral diseases is possible in right and left bundle-branch block, arborization block, right and left ventricular hypertrophy, atrio-ventricular excitation (short PR interval and long QRS time—Wolff-Parkinson-White syndrome), acute cor pulmonale. In the presence of acute ventricular involvement there may be low voltage, slurring or prolongation of the QRS complex, depression or elevation of the ST segment, flattening or inversion of T waves. The most frequent abnormalities are in the T waves, but their alterations are labile and the least specific features of the electrocardiogram; the T wave may be affected by a great variety of factors including the tone of extrinsic cardiac nerves. The changes in the ST segment usually, though not always, correspond to acute muscle lesions, they are rarely permanent and indicate anatomical or biochemical damages. In acute myocarditis with strong evidence of viral etiology, clinical and electrocardiographic findings were even those of coronary occlusion (Gillis and Walters).

Prolonged QT interval signifies a diffuse myocardial disturbance. The differentiation, electrocardiographically, between pericarditis and myocarditis is often difficult, if not impossible, these conditions may all develop together Pericarditis may also exist without any electrocardiographic abnormalities Serial electrocardiograms are important since the inflammatory lesions are often transient although occasionally the abnormalities may last for weeks or months. In patients with virus pneumonia or Bornholm disease pericarditis may only be recognized with the aid of serial electrocardiograms

In low grade viral infections such as infectious mononucleosis, interstitial infiltrations seen in the heart are compatible with conductive changes demonstrable by the electrocardiogram in the assumption that the infiltrations may occur in any part of the cardiac muscle and may also involve important conduction fibres (Allen and Kellner). In many cases

Sudden or unexpected death, *especially in infants, is sometimes caused* by acute viral myocarditis; this would have been overlooked had not the heart been carefully examined histologically. Myocarditis was observed in infants and children dying during outbreaks of poliomyelitis; cardiac *damage has been also found in association with inflammatory changes in* the meninges in encephalomyocarditis virus infection or with interstitial pneumonia caused by viruses of the psittacosis-lymphogranuloma group or undetermined viruses.

Myocarditis *in* viral diseases often manifests itself in a subclinical form. The importance of its recognition lies in the fact that with the knowledge of its presence it may be desirable to extend the period of convalescence in order to prevent the occurrence of myocardial residuals in mumps (Bland), poliomyelitis (Spain, Bradess and Parsonett) and measles (Ross); infectious mononucleosis (Kalk and Ulbricht, Leibowitz), influenza (Lyon) and epidemic hemorrhagic fever (Barbero, Katz, Kraus and Leedham).

Viral diseases (i e measles, poliomyelitis, mumps, varicella, infectious mononucleosis, viral hepatitis) may give rise to slight focal inflammatory lesions in the heart which *do not produce clinical manifestations.* Healing of such myocardial lesions might leave focal myocardial fibrosis in patients with no history of previous rheumatic diseases or other cardiac lesion and might also account for otherwise unexplained benign bundle-branch block (Hackel)

The results of histopathological studies in the cardiovascular sphere of viral diseases remain valuable. A cardiotropic or cardiotoxic virus may cause cardiovascular damage especially interstitial myocarditis or damage *to myocardial fibres of varying degree.*

* * *

Today, *in* cases of viral diseases, electrocardiographic study *is often* the basis of diagnosis of heart involvement. As a result of increased electrocardiographic examination of patients with infectious diseases the incidence of myocarditis is now regarded to be higher than heretofore Symptoms and *signs of heart disturbances are often slight or absent so that only* the electrocardiographic alterations may be suggestive of cardiac damage. On the other hand very severe cases are known to have shown no or only minor electrocardiographic changes. Evidence of various electrocardiographic abnormalities in fatal or non-fatal cases in various viral diseases demonstrates the existence of myocarditis.

When analyzing the electrocardiograms of patients with viral diseases,

changes of the T waves, has been rendered *doubtful* by some studies (Nickerson, Kühns, Doenhardt). Although we are not in possession of a useful pharmacological test for establishing an autonomic imbalance as the cause of electrocardiographic alterations, the probability of the presence of such disturbances with, or without, organic damage to the heart in viral diseases cannot be denied. The variability of certain electrocardiographic features—the waxing and waning of T waves—may be not only the consequence of the appearing and disappearing of inflammatory lesions but, especially in a late convalescent stage, should make one think of a variable functional factor.

The observed frequent changes of T waves, which have often been confined to chest lead CF_4, indicate that the middle and external layers of the anterior wall of the left ventricle have been mainly affected (Holzmann). According to Leibowitz, the electrocardiographic changes confined to the T wave *in* CF_4 *are not sufficiently meaningful of cardiac involvement.* This change is often seen when the precordial electrode is shifted slightly to the right of the CF_4 position and occasionally even in the CF_4 position. Bramwell and King think that deflection of the T wave in the chest leads in the direction contrary to normal means little in a given tracing, however, a change towards normal suggests that the myocardium has been affected.

Ljung, who, in cases of infectious diseases, warns against putting the signs of equity between pathologic T waves and myocardial damages, assumes that the occurrence of these electrical changes are due to a general disposition to respond *readily to an irritation* of the sympathetic nervous system rather than due to inflammatory changes involving part of the myocardium which are apt to produce electrocardiographic abnormalities. It is not always possible to recognize the chief direction in which nervous regulations are going in a particular case especially if the symptoms are of both sympathetic and parasympathetic nature which implies a simultaneous overactivity of both systems Sometimes an autonomous instability that has always been present prior to the infection prepares the ground for this *reaction* Such persons appear to be predisposed to excessive reactions and maladjustments to various situations.

Non-specific neurovegetative and neurohormonal derangement may sometimes, in connection with various viral diseases, have great significance and may be responsible for some cases of sudden or unexpected death during convalescence. As Wuhrmann says, "to what the sudden death, as

of different viral diseases some delayed atrio-ventricular conduction was found by electrocardiogram but rarely a high degree of heart block.

Right bundle-branch block (Lyon, Ross), complete heart block (Clark), and left bundle-branch block (Guistra and Nilsson) in measles, complete heart block (Logue and Hanson) and permanent auricular heart block (Goldfinger, Schreiber and Wosika) in German measles are important findings. Sinustachycardia may develop in measles and in poliomyelitis Organic damage to the auricles in paralytic and non-paralytic poliomyelitis is no rare occurrence (negative P waves, prolonged PR interval lasting many months) (Frischknecht and Zellweger). Auricular premature contractions are reported in infectious mononucleosis. The syndrome of Wolff-Parkinson-White was found in mumps (Rosenberg) and in poliomyelitis (Frischknecht and Zellweger). An acquired lesion on the basis of circumscribed structural changes of the myocardium may be the cause of this pre-excitation phenomenon.

Specificity of electrocardiographic changes in viral and bacterial myocarditis cannot be established.

The frequency of electrocardiographic alterations in infectious mononucleosis leads up to the question as to whether abnormal electrocardiograms are always due to myocarditis, particularly in view of analogous changes in connection with disturbances of the extracardial autonomous nervous system

In poliomyelitis longlasting electrocardiographic changes may be produced by a viral insult of the autonomous nervous system itself (Frischknecht and Zellweger) Heart involvement in connection with viral diseases may be caused by viral insult or by specific and, more frequently, by non-specific damage to the autonomous nervous system, Manning and Yu go too far in considering all electrocardiographic changes during the course of acute poliomyelitis as non-specific

Autonomous imbalance in viral diseases may lead to longlasting heart involvement. The difficulty in dealing with derangement of neuro-vegetative regulation evidenced by electrocardiographic abnormalities is great. There is no doubt, that neuro-vegetative and neuro-hormonal factors may, in viral diseases, be active in producing a deviation from the normal electrocardiographic findings The effect of the sympathetic and parasympathetic system on the electrocardiogram has been differently judged by various authors. The value of functional tests—i e the ergotamin test—recommended for the distinction between vegetative and organic

of pure hypopotassemia and was not influenced by administration of potassium. In hypopotassemia with hypocalcemia, the QT was prolonged as in hypocalcemia, the degree of merging between T and U increases with increased QT duration. The typical electrocardiographic pattern of hypopotassemia consists of progressing depression of ST segment and inversion of the T wave and increasing amplitude of the U wave in the left precordial leads.

A special feature of the prolongation of the QT in viral diseases is its reversibility after disappearance of the original disease and after normalization of the blood electrolytes and the plasma proteins.

* * *

Biochemical investigations have given some insight into alterations in the metabolism and resulting transitory or permanent incapacity of circulatory physiology during viral diseases. We observe:

1) biochemical changes occurring within the body of patients affected by virus infections as a result of the catabolic phase of injury due to overwhelming action of invading pathogens (Eaton and Bower);
2) greater or lesser degree of metabolic normalization as a result of the anabolic phase of recovery from viral diseases.

Albumins and globulins of the blood plasma are in a certain equilibrium in health, this state of balance is altered during infections.

In the acute stage of infections the serum albumin decreases and the globulins tend to rise. The earlier and more acute the infectious process, the greater is the increase of the α and β globulins (e.g. in poliomyelitis). In subacute and chronic infections, such as infectious mononucleosis, electrophoretic analysis revealed an increase in β and γ globulins. In convalescence albumin increases and globulin reverts to normal. In a number of viral diseases the same or similar alterations regarding serum proteins are observed.

In viral diseases loss of plasma from blood stream occurs as a result of an increased capillary permeability, and this is responsible for a more or less obvious hypalbuminemia. Increased permeability of the vascular tree, probably mainly of the capillary walls, has also been experimentally observed in infections.

Altered permeability of semipermeable cell membranes may also occur if the organism is overflooded by antibodies produced by virus, and the body reacts hyperergically.

Important tissue changes result from the interaction of antigen and

it occurs in acute interstitial myocarditis, is essentially due cannot be said with certainty; probably, in addition to ventricular fibrillation and organic damage to the atrio-ventricular conduction system, neurovegetative factors have to be taken into account." The importance of neurovegetative factors for the heart and circulation is still being underrated. An increased sympathetic tonus exposes the heart more to the danger of coronary insufficiency than a vagal hyperactivity. A predominance of sympathetic activity interferes with the circulatory economy and goes along with a very high oxygen consumption of the heart, even during rest, and draws on the coronary reserve. Hormonal cardiometabolic compounds (Raab) may be involved in the pathogenesis of fatal outcome during the convalescence of viral diseases. Anatomical considerations are not always sufficient to explain such cardiac incidents, they should be supplemented by a biochemical approach

Q-T prolongation has been reported in many cases of viral diseases. It occurs in infectious hepatitis, infectious mononucleosis, poliomyelitis, influenza, measles, and epidemic hemorrhagic fever. Hegglin points out that the prolongation of the Q-T interval is the manifestation of an energetic cardiac insufficiency; an additional shortening of the Q-second heart sound points to an energetic dynamic insufficiency. This syndrome may be found as a secondary complication of a general disease, caused by a disturbance of the myocardium, the contractions of which become weak. Histopathologic alterations of the heart produced by energetic-dynamic cardiac insufficiency were described by Elster (1953)

The Hegglin syndrome may also be considered as a protection reflex of the damaged hypodynamic myocardium Hegglin explained a number of symptoms of energetic dynamic cardiac insufficiency by the Bezold reflex.

The presence of QT segment prolongation in the electrocardiogram is a sign of considerable diagnostic importance. According to Bellet and Finkelstein, this finding is associated with varying degrees of myocardial derangement and disease; a return to normal occurs when the myocardial abnormality is corrected. These authors classified the clinical conditions associated with Q-T prolongation under the following headings: 1) electrolyte disturbances, 2) myocardial abnormalities and/or disease, 3) conditions associated with myocardial anoxia, 4) combined factors, 5) drugs and 6) unknown etiology. Q-T segment prolongation together with characteristic ST and T wave changes is an important diagnostic criterion of diminution in the serum calcium and potassium. Surawicz and Lepeschkin showed that the duration of the QT interval was not prolonged in cases

s secondary. According to Siegmund, the chief object of attack in viral hepatitis is the capillary bed. The parenchymatous and mesenchymal alterations are the sequelae of disturbances of the blood flow and simultaneously changes of the capillary walls. The noxious agent which is responsible for the disturbance of the blood flow in the liver, causes additional direct toxic damage to liver parenchyma. Glanzmann assumes that the center of pathogenic events in viral hepatitis is the inflammation of the liver associated with parenchymal damage and disturbances of permeability i e. serous inflammation.

Although opinions are divided regarding the primary point of attack within the liver in viral hepatitis there is a growing realization that the disturbance in blood flow, the increased capillary permeability with transudation into the tissues and resulting hemodynamic deficiency are important factors in the pathogenesis of this disease.

Wollheim found hypovolemia in patients with viral hepatitis (with and without jaundice). The circulating blood volume is, in hepatitis, reduced owing to loss of plasma. The increased permeability of capillary walls—similar to events in states of shock is, in viral hepatitis, limited to the liver.

In the general shock syndrome the whole splanchnic area is considered to have an increased capillary permeability. The deficit of plasma in severer cases of viral hepatitis is associated with depressed levels of serum albumin. Edema of legs and ascites in such cases are related to lowered serum albumin and decrease of osmotic pressure, but the hypalbuminemia is not usually the only factor responsible for the development of ascites. There may be increased portal pressure due to scarring or to altered reconstruction

In severe hepatitis hemorrhagic complications are not rare; at the same time decreased capillary resistance and plasma alterations are demonstrable. The tendency to hemorrhages and increased capillary fragility may be caused by an increase in serum globulin fractions (Martini and Engelkamp).

The frequency of bradyuria and oliguria in the acute stage of viral hepatitis was explained by Wollheim as being due to insufficient renal blood flow causing tubular insufficiency.

The Capillary Syndrome in Poliomyelitis

The poliomyelitis virus reaches the alimentary tract by pharyngeal secretions and/or feces and may, for several weeks, be found in the stools

antibody. In virus diseases there may be structural changes of tissue caused by viral action and by *hyperergetic response to the virus*. Klemperer wrote: "It is evident then that even in the relatively simple experimental anaphylactic or Arthus phenomenon type of hypersensitivity, the tissue lesions are not of diagnostic value. In other words, the microscope does not reveal the allergic mechanisms of the structural alterations; at best it is only suggestive. How much more complicated is the situation in the type of hypersensitivity which develops in the course of infections with living microorganisms, not to speak of viruses." Considerable clinical evidence, pathohistologic findings and some experiments in viral infections point to capillary alterations which may produce transudation, and as a consequence damage to adjacent parenchymal tissue and sometimes hemodynamic deficiencies This protein leakage into the tissues is a capillary syndrome. It may be explained by examples of some different diseases.

The Capillary Syndrome in Viral Hepatitis

Viral hepatitis occurs in two main forms: infectious hepatitis = hepatitis A, and serum (hematogenous) hepatitis = hepatitis B. The absence of cross immunity between the two viruses A and B indicates antigenic differences They are different entities despite their identical clinical and pathohistologic manifestations

Histologically, biopsy findings in viral hepatitis are rather typical. There is liver damage especially in the central parts of liver lobules involving single or groups of cells, accompanied by mesenchymal reactions such as proliferation of Kupffer cells and portal and lobular infiltration with predominantly mononuclear cells and a small number of eosinophil leucocytes A peculiar form of degenerative liver cells, the "acidophil cell," is frequently observed in viral hepatitis The subsiding phase of viral hepatitis is characterized by portal infiltrates and regeneration of parenchymal cells. In Thaler's opinion, the causative agent of viral hepatitis is an epitheliotropic virus, information of what happens in the early stage of hepatitis is scarce. The swelling of liver cells leads to compression of the capillaries of the lobules which—especially in the acute stage of hepatitis—causes severe disturbances of the blood flow These alterations in blood flow are the chief cause of the destruction of cells of the central parts of the hepatic lobules The swelling of the liver cells is regarded as the expression of a severe cell damage which favors further destruction.

Voegt regarded viral hepatitis as a primary capillaritis, the hepatosis

tendant inflammatory process. Dieckhoff also draws attention to the enormous edema and hyperemia in the anterior horns of the spinal cord in poliomyelitis. This edema can remain for months.

Doering recently pointed out that poliomyelitis is not merely a question of nerve cell involvement; it is a problem of the whole nerve tissue. Intracellular protoplasmatic and subsequent karyoplasmatic alterations caused by direct viral action result in destruction of neurons; *these happenings* are not more important than other intricate events within the whole nerve tissues affected by poliomyelitis infection.

Bower, Eaton, Chudnoff, Affeldt and Chaney, and later Routh and Paul, found decrease of the albumin content of the plasma parallel to the severity of acute poliomyelitis cases It has been assumed that the lowered serum albumin in poliomyelitis and the accompanying marked urinary nitrogen excretion may lead to shock and circulatory collapse.

In poliomyelitis the degree of destruction of specific neurons may be due to direct viral action and to edema as the sequelae of circulatory disturbances and, possibly, of lowered serum albumin.

The Capillary Syndrome in Smallpox

Classic (variola major) and mild (varioloid) smallpox are the same viral infection. Between the viruses of variola major and minor and the viruses of cowpox and vaccinia only minor differences (serological and immunological) can be elicited Cross immunity tests in monkeys with the viruses of variola and vaccinia have shown that the two are closely related immunologically Facts referring to vaccinia apply to the virus of smallpox Hassko observed, in experimental vaccinia infection of the rabbit, that there was almost regularly an increased capillary permeability of internal organs Stimson thinks that the virus of smallpox apparently produces a toxin which gives rise to the constitutional symptoms and fever especially at the invasive stage but which also has a vasomotor and angiolytic effect evidenced by the initial petechial rashes and by the hemorrhagic forms of the diseases Gins speaks of a toxemic component of the variola-vaccinia virus by the hemorrhagic tendency of this illness. Wolman, who used the Feulgen reaction in the histologic study of human smallpox material, found inclusion bodies and extracellular virus aggregated within the endothelial cells lining the blood vessels of various organs and in the lamina propria of the mucosa of the mouth and esophagus The virus might have become fixed within the sections in various

and on the intestinal mucous membrane. Bodian suggested that multiplication of poliomyelitis virus in the body may occur in at least three different phases which he referred to as the alimentary, vascular and neural phases. From the portal of entry, i.e. the alimentary tract, the virus goes into the lymph channels, the blood stream, and may spread to the central nervous system. But the paralytic cases are of high concern for the physician. *Today severe poliomyelitis is no longer a disease with merely a* selective affinity for certain nerve cells of the spinal cord but a diffuse illness with involvement of various parts of the brain, the spinal cord, the sympathetic ganglia and extraneural substrates. Viremia is an essential stage in the dissemination of virus through the body with invasion of the central nervous system as a secondary phenomenon. According to Bodian, the virus is *present in the blood in abortive human cases* and in the preparalytic period of the disease in chimpanzees after virus feeding; invasion of the central nervous system may occur by way of the blood stream, rather than by way of nerves, and the poliomyelitis virus can be cultivated in tissue culture in the absence of nervous tissue

According to Kalm, *preparalytic cerebral invasion in poliomyelitis* occurs within the vegetative centers. Cord lesions develop almost at one and the same time and successive involvement of spinal foci is the exception. Lesions of poliomyelitis consist of neuronal necrosis which excites considerable secondary reactions among the various types of mesodermal cells participating in inflammation. As against the *generally recognized highly neuronotropic property of the poliomyelitis virus*, it is a fact that a multitude of tissues may be attacked or may react in poliomyelitis infections.

The role of edema of the central nervous system is, according to Bower, Eaton, Chudnoff and Chaney, a concept that has ebbed and *flowed, never having been either conclusively accepted or disproved* Severe paralysis may occur without important vascular involvement or severe leucocytic infiltration of the cord On the other hand, the presence of edema in the central nervous system affected by poliomyelitis and its significance for clinical symptomatology *has already been stressed fifty years ago by some* physicians. Edema is ordinarily a conspicuous feature of sections and, in poliomyelitis, is the only pathological reaction of the central nervous system against which any therapeutic measure is effective (Stimson, 1947). According to Bower, Chudnoff, Affeldt and Chaney, a certain amount of focal edema is initiated by *the action of the causative virus* and the at-

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fragility tests, the microscopic hematuria and albuminuria, i.e. renal capillary involvement. Partial or complete renal failure may occur. According to Earle, abnormalities of small vessels appear to be the chief characteristics of the early phases of hemorrhagic fever and may set the stage for subsequent development. Arteriolar dilatation is responsible for the hypotension of hemorrhagic fever, but in addition circulating blood volume is reduced through loss of plasma by way of damaged capillaries. *Capillary damage is the basic process* (Steer and Hullinghorst).

These few examples may suffice to show the importance of the capillary syndrome for the pathogenesis of many viral (and rickettsial) diseases. The effect of direct viral action of susceptible cells should not be neglected for the understanding of the whole pathogenetic situation. Siegmund considered the direct toxic effect of virus on the liver parenchyma as additional. On the other hand, in Thaler's opinion, which recognizes the disturbances of blood flow as essential for the destruction of hepatic cells, the point of attack of the causative agent and the primary site of viral hepatitis is the liver cell. In poliomyelitis, too, with all due respect for the pathogenic importance of circulatory disturbances, the direct neuronotropic action of the virus should not be underestimated. The damage, caused by yellow fever virus *in whatever organ it may be present*, is essentially a selective necrobiosis of epithelial cells of the liver, kidneys and myocardial fibres; the mesenchymal cells are not involved. Death results from the physiologic incapacity of the liver or kidneys or both or from cardiac damage (Bugher) But according to Craig the yellow fever virus has also a marked effect upon the integrity of the capillaries; there are early capillary congestion and hemorrhages which are more severe in the later stages of the disease

It may be assumed that direct viral action on host cells and/or the sequelae of a disturbed blood flow, i e. transudation of circulatory fluid plus its oncotic chemicals cause damage to various tissues in different viral diseases Sometimes there is merely a functional capillary damage associated with transudation in tissues; this is reversible. In other infectious diseases clinico-pathologic evidences point to certain capillaries as the site chiefly involved by the disease. Damage to the pulmonary capillary bed and capillary leakage lead to interstitial pneumonia or pneumonitis in influenza, virus pneumonia, interstitial pneumonia of infants, measles, varicella and psittacosis.

The extent of changes in the serum albumin and serum globulin con-

stages of its migration from the blood stream to the epidermal layer. According to Bras, the damaging agent of smallpox selects certain capillary groups; the epithelial damage or lesions in other tissue appear only in areas vascularized by those capillaries. In severe cases of smallpox there is a tremendous loss of circulating body fluid and intensive toxic destruction of protein. Increased permeability of capillaries leads to the escape of protein and electrolytes through the capillary walls into the tissue spaces, to profound and consistent loss of plasma, and subsequently to hemodynamic deficiency, peripheral circulatory failure and death.

The Capillary Syndrome in Epidemic Hemorrhagic Fever

Hemorrhagic epidemic fever is a disease of unknown etiology, probably of viral or rickettsial origin. The chief manifestations are febrile, cardiovascular, gastrointestinal, renal, hemorrhagic and occasionally neurological. Almost every system in the body is involved in some manner or other (Powell). The clinical manifestations of the disease occur in phases described as the invasive, toxic and convalescent stage. According to Leedham, it is entirely possible that this disease is caused by a virus which has an affinity for the endothelial cells of the cardiovascular tree. In the viremic stage this agent may produce severe systemic reactions which characterize the invasive stage. By the time immunity has developed to the point of successfully combatting this agent, cellular invasion has produced cellular damage with resulting increased capillary fragility and hemorrhages of the toxic hemorrhagic phase. By the time the endothelial cells have regenerated sufficiently to re-establish the integrity of the capillary tree, the hemorrhages have receded. There may be a gradual return to normal.

According to Barbero, Katz, Kraus and Leedham, considerable clinical evidence points to the capillary as the site principally involved by the disease. In the first few days of illness, the facial flush and mucous membrane injection indicated a general capillary dilatation. Abnormal capillary permeability was indicated by presence of edema in the preorbital, facial, conjunctival and retroperitoneal tissues The elevation of the hematocrit reading and hemoglobin content during the first few days of illness may be manifestations of the escape of plasma through the capillary walls as well as of simple dehydration. The vascular instability and shock may also be related to capillary involvement. Other manifestations of capillary damage were the petechial hemorrhages, the positive capil-

convalescent stages, i e. the diuretic phase, non-protein nitrogen comes down. Occasionally diuresis *leads to salt and potassium loss.*

Potassium is the dominant cationic component in protoplasma; its intimate relation to the alterations finds its expression in biochemical findings in cases where toxic destruction of protein is large. But little information regarding electrolytic and other metabolic changes in viral diseases is available

* * *

Changes in cardiovascular concepts of viral diseases brought a greater broadness of perspective New concepts about cardiac and vascular manifestations and complications have opened the path for an ever increasing improvement of treatment even in persons severely ill from a viral disease.

In some viral diseases of the psittacosis-lymphogranuloma venereum group, modern antibiotic therapy is effective and has greatly improved the prognosis of these illnesses.

Peripheral circulatory failure in severe infections may be due to decrease in blood volume and/or to loss of vasomotor and venomotor tone. Restoration of the blood volume by transfusion is necessary to relieve the deficiency in combination with restoration of venomotor or vasomotor tone by norepinephrine infusion Restoration of blood volume by transfusion will not completely relieve the disorder if venomotor and vasomotor tone are lost, nor will restoration of vascular tone, by norepinephrine infusion give complete relief if the blood volume is greatly reduced (Dock). Norepinephrine 2 mg is given by slow infusion in 500 cc. of 5 per cent glucose intravenously The infusion may be spread over many hours.

Treatment aiming at the prevention of collapse in severe viral infections is considered a very important line of therapeutic approach, at the same time being an efficacious treatment for a possibly existing myocarditis In peripheral circulatory failure, the circulation cannot be improved merely by digitalis or strophanthin, camphora and caffeine.

Fluid management is very *important in* bulbar poliomyelitis and epidemic hemorrhagic fever because of the danger of pulmonary edema. Low serum potassium found in patients with severe poliomyelitic paralysis or with bulbar involvement and in the convalescent *diuretic stages of epidemic* hemorrhagic fever returned to normal on administering potassium.

The capillary syndrome in viral diseases can be influenced therapeutically Cases of viral hepatitis and poliomyelitis are benefited by plasma and whole blood infusions In the treatment of epidemic hemorrhagic fever concentrated human albumin has been very effective (Katz, Leed-

centrations has been stressed. The role they play in viral diseases, how ever, is rarely sufficient enough to reverse the albumin/globulin ratic Other pronounced biochemical alterations occurring in viral diseases ar present but, in general, little attention has been paid to the metaboli aspect of viral diseases.

Large losses of nitrogen and potassium have been observed in polio myelitis. According to Bower, Morgan and Chaney the acute catabolic phase of poliomyelitis is characterized by excretion of nitrogen and potassium in the urine and by a fall of serum albumin. Serum potassium values may range from subnormal to very high levels. It is the abrupt drop in serum albumin and the accompanying marked urinary nitrogen excretion which may lead to shock and peripheral vascular collapse in severe cases of poliomyelitis. The characteristics of the subsequent subacute catabolic phase are similar to those of the acute phase but less marked. There is a continued excess of excretion over intake for potassium and nitrogen but at a lesser rate. Serum albumin remains low but may rise gradually while globulins are elevated, with serum potassium in the normal range, unless intake is abnormally low The anabolic phase is characterized by positive balances of potassium and nitrogen. Serum albumin values approach normal in mild and moderate cases but may, for months, be low in severe cases. Serum globulins remain elevated and potassium levels are normal except when intake is insufficient to meet the demands of tissue synthesis. In time of increased potassium excretion and inadequate intake, potassium deficiency may occur which may accentuate muscle paralysis and may cause cardiac damage and adynamic ileus. Particularly in respirator patients extensive electrolyte changes may be produced in body fluids. Patients with bulbar poliomyelitis cannot tolerate superimposed hypopotassemia. Complications in poliomyelitis attributed to other causes are due to increased metabolic loss of potassium through the kidneys.

In severe cases of viral hepatitis, correlations are found between clinical and biochemical findings. In very grave cases progressive decrease of serum albumin, of the total cholesterol and cholesterolester blood levels, hypoglycemia, progressive reduction of urea blood levels and inadequate estrone inactivation have been demonstrated (Zondek and Bromberg). In epidemic hemorrhagic fever during the toxic (oliguric) stage, non-protein nitrogen, phosphate, creatinine and potassium levels increase while ionized calcium and carbonoxide combining power decrease. Variations in blood-urea nitrogen follow those in non-protein nitrogen. In the

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ham and Kessler). In severe smallpox the treatment with plasma and whole blood infusions usually comes too late to be helpful. In severe varicella pneumonitis intravenous plasma has been successfully used.

The treatment of several viral maladies showing the capillary syndrome and its sequelae with plasma expanders has the object of increasing and maintaining the circulating blood volume and to bind or absorb toxins. Plasma expanders are inexpensive, completely sterilizable, non-antigenic and well tolerated. They include dextran and synthetic colloids such as the polyvinylpyrrolidones (PVP)—Kollidon, Periston, Plasmosan, Periston N.

Dextran is a polysaccharide manufactured from sucrose by a fermentation process. The coccus leukonostor mesenteroides produces an exocellular enzyme which polymerizes glucose into a polysaccharide forming, as the end product, dextran. The molecular weight of dextran varies from 50,000 to 100,000, averaging 65,000

Promising are the plasma substitutes, the synthetic colloids, Periston and Periston N. There are differences between Periston and Periston N. Both are polyvinylpyrrolidone, which is a polymeric substance of the repeating unit vinylpyrrolidone. There exists a correlation between viscosity and average molecular weight of a mixture of polyvinylpyrrolidone, the correlating factor is called the "K" value. Peristone contains PVP with colloidal molecules which are even unable to penetrate the damaged vascular wall (mean molecular weight of 40–50,000), while Periston N contains a polymer of a mean molecular weight of 12,600 enabling a rapid and complete excretion through the kidneys. Periston is first and foremost a plasma expander with a sufficient retention period in the vascular system. Periston N is perhaps a means of detoxicating the body; the kidneys serve as organs of excretion of toxic substances (Schubert). The ability to influence the edema of the central nervous system and to detoxicate the body has been ascribed to both Periston and Periston N are not considered antigenic and may exert no ill effects on the liver and kidney functions. Long term storage by the body is excluded if *usual* doses of Periston are administered. Periston has been used in viral hepatitis; Periston N in poliomyelitis, viral hepatitis, influenza, encephalitis. The use of these colloidal blood substitutes for the treatment of the capillary syndrome in severe viral infections seems to be a real advance

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PART TWO

CHAPTER III

Exanthematous Diseases

1. Measles

Measles (morbilli) is an acute contagious disease which is characterized by conjunctivitis, exanthema in the mouth (Koplik's spots), fever and a typical eruption. In most cases, measles is not a serious disease; but death may occur due to severe bacterial infection, bronchopneumonia, encephalitis or some other complications.

The cause of measles is a filterable virus which is present in the blood and in the nasopharyngeal secretions during the whole prodromal period and during the 24 to 48 hours following the appearance of the rash. The period of incubation of measles is ten days The prodromal stage before the appearance of the maculo-papular exanthema is four days. The eruption lasts three to five days.

Pulmonary involvement is a very frequent occurrence; many cases show pneumonic infiltrations in successive roentgenograms where no definite physical pulmonary signs can be demonstrated

Pathologic lesions of measles consist of the multinucleated giant cells of Warthin and Finkeldey in the lymphoid tissues, tonsils, pharyngeal mucosa, thymus and viscera The exanthema starts with exudation of serum and proliferation of endothelial cells in the vessels of the upper portion of the cutis The exudate spreads into the epidermis leading to vacuolization and necrosis of the epithelial cells and vesicle formation. Desquamation of the superficial layers of epithelium of the skin follows. Small perivascular round cell infiltration with congestion and edema is present in the skin, the mucous membranes of the eyes and the respiratory system The presence of parakeratotic cells with intranuclear and acidophil inclusions has been described as a pathognomic characteristic of the measles eruption

In the lungs there is bronchitis with congestion of capillaries, a mononuclear interstitial peribronchial infiltration with edema and congestion and an interstitial infiltration of alveoli Autopsy findings in encephalitis

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Clinical and/or electrocardiographic findings suggestive of cardiac disturbances in measles from 1912 to 1952 were reviewed by Ross (1950). Hecht (1912) reported a case of a three-year old child who showed conduction disturbances in an electrocardiogram taken during the third week after she had had measles, perhaps complicated by influenza.

Eyster and Middleton (1920) reported a case of auriculoventricular heart block following measles and inflammation of the heart valves. Neubauer (1944) noted the presence of myocarditis during the febrile stage of measles in four patients who also had bronchopneumonia.

A patient reported by Lyon (1946) first felt irregular beating of the heart when he had measles at the age of 39, he had paroxysmal bouts of tachycardia during the following two years, at the end of which an electrocardiogram was taken and right bundle branch block, left type variety (Wilson) was found. Electrocardiograms taken later on different occasions always revealed the same right bundle branch block. Episodes of rapid heart beat accompanied by a feeling of discomfort in the heart region and slight pain in the precardial area occurred frequently.

Clark (1918) reported three cases of complete heart block in three children, possibly attributable to measles One case had frequent Adams-Stokes seizures and died two years after the onset of heart block.

Giustra and Nilsson (1950) described the case of a five and one-half year old boy, who showed ventricular (or supraventricular) tachycardia with bundle branch block in an electrocardiogram recorded thirteen days after the onset of measles Tracings taken during the subsequent half year showed shortened and prolonged PR intervals, left and right bundle branch block. The teleroentgenogram showed generalized enlargement of the heart involving all chambers Episodes of rapid heart beat occurred sometimes but subsided within a few hours Giustra (1954) reported that three years after the initial observation this child died during a convulsive seizure which accompanied an attack of tachycardia The autopsy findings relating to the heart revealed a generalized subendocardial sclerosis and focal fibrosis in the left bundle branch. The dilatation and hypertrophy of the heart was more pronounced on the right side. There were no myocardial changes. Giustra concluded that the changes in the heart were due to an infectious process rather than a developmental aberration

Fine, Brainerd and Sokolow (1950) found that two patients in a group of eight with measles had borderline electrocardiograms. Ross (1952)

showed perivascular hemorrhages and collars of round cells. Brain edema may be responsible for symptoms and deaths.

There are few references in the literature on pathologic findings in the heart of fatal cases of measles. Albert pointed out that not only slight inflammation but even extensive infiltrations were sometimes seen microscopically in the hearts of patients with measles. These changes, however, were not found before the ninth day of illness. Of ten hearts of patients with measles two showed myocardial lesions, three had foci of pericarditis and five revealed no abnormalities.

Degen described the findings in one hundred autopsies of patients who died from measles. There were four instances of pericarditis and four showed evidence of lymphocytic infiltration in the myocardium, frequently perivascular in distribution.

The occurrence of myocarditis in measles, according to clinical observations was reported in the literature from the year 1911 to the year 1930. Accidental heart murmurs during the period of convalescence, irregularity of the heart beat and an abnormally low pulse rate have been observed. If measles was accompanied by complications such as bronchopneumonia and nephritis, then secondary heart involvement with dilatation and cardiac insufficiency were frequently observed.

Strong thought that the heart was not so commonly involved in measles as in other infections. An occasional tachycardia or disturbance of rhythm may be noticed during the disease and endocarditis and even pericarditis have been known to occur as sequelae. Brinker emphasized that if a community has for a long time escaped measles the course of the epidemic is often more malignant. In an epidemic of measles in Southern Greenland (1952) heart failure was the most serious complication and accounted for eighteen cases (i e. 22 per cent of all complications) One third of the deaths were due to heart failure. Thirteen of these eighteen cases occurred in females, four of whom were pregnant or puerperal. Heart failure occurred mainly in the older age classes, with only one case in the age group of 15 to 34 years (Christensen, Schmidt, Bang, Andersen, Jordal and Jensen).

The earliest report on heart block due to measles was made by Burzi in 1903. This author described a case of complete heart block with low pulse rates and Morgagni-Adams-Stokes seizures occurring as an attack of measles was receding. The heart block was transient and the patient recovered.

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2. German Measles

German measles (Rubella) is an acute contagious disease characterized by fever, catarrh, tenderness and enlargement of lymph glands, absence of Koplik's spots and a rash consisting of diffusely distributed pink macules. The exanthema lasts for two or three days, the lymphadenopathia may persist for two or three weeks. The incubation period is twelve to twenty-one days. If catarrh precedes the rash the patient is probably contagious for two days before the appearance of the eruption and the period of infectivity is over by the time the rash has disappeared. The generalization of the disease is limited to the same period of time. Throat washings obtained at that time contain the virus, and German measles has been transmitted to susceptible volunteers by spraying the upper respiratory tract with this material. The incubation period in human subjects infected by inhalation ranges from nine to sixteen days until the appearance of the rash and lymphadenopathia precedes the rash by up to six days in some instances. There is no evidence that the artificially induced disease differs in any way from natural rubella and the immunity should be equally effective.

The average age of the patients is higher for rubella than for measles. Many school children and students contract the disease. After the year of forty, German measles is rarely met. The disease is usually mild but

made a study of one hundred and twenty-five electrocardiograms of seventy-one children hospitalized for measles. The following electrographic findings (probably abnormal) were: complete right bundle branch block, QT_c value above 0.430 a high incidence of R^1 wave in lead CF_2 and a markedly prolonged PR interval. The PR interval was longer than the Ashman and Hull standards in thirty per cent of the electrocardiograms and was significantly prolonged in twenty-nine per cent of them Although there were no electrocardiographic records of these children prior to measles, it was presumed the disturbances developed during the course of the disease. The high incidence of R^1 waves in lead CF_2 occurred more commonly in measles than in other acute illnesses. Prolongation of QT_c and of PR intervals in the records of children with measles were the result of myocardial involvement. In the relatively few follow-up examinations which were made, it was found that the abnormalities did not subside by the time children usually resume full activity after having measles.

Ross noted a systolic murmur at the third or fourth intercostal space along the left sternal border or near the apex on at least one examination in forty-two per cent of the children The murmurs were interpreted as functional. Diminished intensity or poor quality of the apical first heart sound was noticed in sixteen children at the time their electrocardiograms were taken; a metronomic rhythm was present in two children. Eighty-three percent of the records taken of children with a soft or poor first heart sound (with a second sound of normal intensity) or a metronomic (tic-tac) rhythm had a R_1^1 wave in CF_2 and/or prolonged PR interval. Other symptoms and clinical symptoms of myocarditis were not noted.

It may be supposed that many patients ill with measles had secondary bacterial infections. It is difficult to tell whether any of the cardiac pathologic changes were attributable to the measles virus (Ross). Lyon also thought that it may be supposed that streptococcal infection of the upper respiratory tract coexisted during measles or later and that it was responsible for the resulting myocardial lesion. Obviously we are unable to give a satisfactory explanation concerning this point.

Ross recommended to extend the period of rest after measles, especially for children under eight years of age, in whom a higher incidence of electrocardiographic disturbances was found than in the older children

It appears worthwhile to advise a patient suffering from right bundle branch block to restrict his activities and to warn him to avoid major exertion (Lyon).

Anderson (1950) who collected from the literature 44 cases of maternal rubella in the first trimester found 22 defective infants. When the illness occurred in the second trimester, three of 22 infants were affected and in the third trimester, 2 of 14.

Morgan, Burnet, Loriman and Bryce (1950) suggested a defect rate between twenty-five to fifty per cent for rubella in the first three months of pregnancy.

In 136 cases analyzed by Conte, McCannon and Christie (1945) 72 per cent had cataract, either unilateral or bilateral, 61 per cent were mentally retarded and 58 per cent had congenital heart disease. At least 53 per cent had multiform anomalies.

In Swan and Tostevan's series (1946) of 37 infants with defects due to maternal rubella, the abnormalities were found in the following order: deafness and mutism, 26, cardiac defects, 19, microcephaly, 2; mongoloidism, 11; other abnormalities, 6.

In cases collected by Patrick (1948), the most frequently encountered abnormality was deafness, followed by heart disease, mental deficiency and cataract.

According to Wesselhoeft (1945), 656 congenital anomalies after rubella of pregnant mothers could be specified as 310 eye defects, 281 cases of deafness, 296 cases of heart defects, 98 of microcephalus, 79 of mental retardation and 22 of dental defects.

Abel and Van Dellen (1949) reported on eighty-four babies (including two sets of twins) born to rubella-infected mothers. Three children were stillborn, their mothers had rubella in the first trimester. Of the 81 living children, 25 were normal and 56 abnormal. The anomalies were: congenital heart disease, 19, congenital cataracts, 14; mental deficiency, 7; and malformed teeth, 5.

Bass (1952) found in nine infants with the rubella syndrome, 8 showing ocular defects (7 cataracts, 2 glaucomas); 6 were mentally retarded and five had cardiac diseases.

Gibson and Lewis found that of 1633 children with congenital heart disease, 17 were born to mothers who had had German measles during pregnancy. Diagnosis of patent ductus arteriosus was considered in 14 of these children and was confirmed in 10 during the operation. An additional cardiac malformation was found in 4 of these patients who were operated on, which indicates that complications are most frequent in these patients. In the only cyanotic child, physical signs, roentgenograms, electrocardiograms and fluoroscopic findings were typical of tetral-

somewhat more severe in adults than in children. Second attacks of German measles are extremely rare.

Some epidemics of rubella are characterized by larger proportions of cases in which complications (i.e. thrombocytopenic purpura) occurred, suggesting that it might have been due to an unusually virulent chain of virus. German measles is occasionally complicated by meningoencephalitis.

Cardiac complications in German measles are not frequent. Logue and Hanson (1935) reported complete heart block and Goldfinger, Schreiber and Wosika (1947) described a case of permanent 2:1 auricular-ventricular heart block following rubella. Much interest has been focused on the occurrence of congenital defects in children born to mothers who had German measles during pregnancy. Gregg in 1941 discovered the relationship between the occurrence of maternal rubella and of fetal abnormalities especially the frequency with which a large number of congenital cataracts followed the maternal infection with rubella. Gregg stressed the danger of the diseases for the fetus and found also associations of congenital cataract with cardiac and other lesions.

Infants born from mothers who have contracted rubella during pregnancy show the following congenital abnormalities.

Eyes: Cataracts (unilateral, bilateral), microophthalmos, buphthalmos, uveitis, dacryostenosis, glaucoma, strabismus, retinal pigmentation.

Ears: Deafness with secondary mutism due to loss of cochlear function.

Heart: Septal defects, patent ductus arteriosus.

Brain: Microcephaly, mental defects.

Teeth: Dental anomalies (retarded eruption, enamel hypoplasia.)

These defects may occur singly or in combinations. According to Bass, rubella in the pregnant mother may result in abortion, stillbirth, a deformed child or a normal child.

Swan and his collaborators have stressed that the fetus was defective in almost 100 per cent of the cases when the mother had rubella during the first six weeks. Later, it became apparent that the data had been obtained from a study of defective children and a lower figure is prevalent when the question of fetal damage resulting from rubella in the first trimester is approached from the angle of the mother's pregnancy (Bass). But the relation of congenital abnormalities of infants to the occurrence of maternal rubella in the first trimester always remains striking. Ingalls and Gordon (1947) assume that about thirty-two per cent of congenital abnormalities are caused by rubella in the first three months of pregnancy.

of the five hearts examined the following defects were found: open intraventricular septum, absence of septum secundum and, twice, a rudimentary septum secundum. According to Toendury and Nick, rubella produces disturbances of active proliferation and differentiation in the lens, in the organ of Corti and in the teeth but causes merely arrest of development within the heart which leads to cardiac defects. The heart does not show differentiation of such an outstanding degree as, for example, does the lens According to Toendury embryopathias are not limited to the rubella infection, the viruses of mumps, viral hepatitis, and poliomyelitis may have the same "teratogenic" effect. These viruses may also attack the epithelial tissues of the embryo and produce disturbances of the growth of the fibres of the lens The high figure of serious damage to the unborn child following maternal rubella is disquieting. Although it is not possible to fix accurately the chances of a baby proving abnormal when born to a woman who had rubella in the early months of pregnancy, the question of therapeutic curettage in cases of rubella in pregnant mothers must be considered It has been stressed that many mothers are suffering from mental stress of waiting six months with the fear of bearing a defective child If German measles is contracted after the fourth month of pregnancy, it can be confidently stated that the child will be healthy and that the pregnancy has to proceed In many cases, the situation should be made clear to prospective parents who must be given an opportunity of sharing the responsibility of deciding whether the pregnancy ought to be terminated (Abel and Van Dellen)

The decision on abortion is not easy and is involved with legal, social and religious implications Bosatra thinks that induction of abortion is unjustified because maternal rubella occurring during the first four months of pregnancy has not resulted in rubeolic embryopathy in 100% of the cases The best solution would be for every girl to have rubella before she is married One attack of rubella usually induces immunity to the disease, and may prevent a disastrous effect on the child Therefore we have to find a means of immunizing girls before marriage. Unmodified virus seems to be suitable, and the problem is to provide this in a form that may safely produce infection and immunity. Physicians should take the opportunity of exposing susceptible girls to a German measles case. It may be prudent that women who had rubella and consider themselves immune should avoid exposure to this disease when pregnant. This last precaution is advised by Schick It is always possible that the mother's

ogy of Fallot. In one child, defect of the ventricular septum was considered, but the lesion was probably not associated with the illness of the mother since she had German measles during the fifth month of pregnancy.

Several instances have been reported in which the mother contracted rubella before conception and gave birth to infants with congenital abnormalities (Wesselhoeft 1947). There are cases of the rubella syndrome in children whose mothers were exposed during early pregnancy without having a noticeable rash. These mothers had German measles in a subclinical form.

Abnormalities of infants following maternal rubella are caused by damage to active fetal proliferation and to differentiation of tissues (Toendury). These alterations represent embryopathias, they are diseases of the embryo during the intrauterine life produced by invading rubella virus.

According to Toendury, the virus reaches the fetus from the maternal bloodstream; it penetrates the intact chorioepithelium which arises from a single layer of ectodermal cells, enters the fetal circulation and spreads through the body of the embryo The virus does not attack the whole organism. Only certain organs are preferably infected and damaged: the lens, the epithelium of the inner ear, the enamel layer of the teeth. There is an evident organ-affinity. The destruction consists of dismixture in drops and vacuolar degeneration of the cytoplasma with subsequent pyknosis of the cell nucleus It does not appear at the same time in the above mentioned organs. Seventeen days after the onset of maternal rubella the fibers of the lens already show degeneration whereas it is not until two hundred and twenty-two days after the mother has been infected by rubella that the sensory cells of the inner ear and the cells of the enamel layer of the teeth are visibly destroyed. According to Toendury, the virus attacks the epithelial cells of the lens, the auditory vesicle and the enamel organ in the early embryonic stage and multiplies there, only when the cells have reached the state of differentiation which is associated with great metabolic activity, is cell destruction caused by the virus Rubella has specificity for the phase of fetal life regarding its localization within different organs (phase specificity, Toendury) Then, it interferes with the metabolism of cells and produces hyaline droplets of cytoplasma and cellular pyknosis.

Nick studied five hearts of human embryos whose mothers had been attacked by rubella between the 35th and 51st day of pregnancy. In four

from those of vaccinia. The antigenic structure of variola virus is similar to that of vaccinia. Both release soluble antigen in infected tissue and both viruses produce a hemagglutinin which is distinct from soluble antigen (Downie and Macdonald).

The smallpox virus enters the body through the mucous membranes of the upper respiratory tract with subsequent transient viremia and infection of the reticuloendothelial system and lymphatic tissues. The virus multiplies intracellularly during the incubation period which lasts about 12 days. A second intense viremia, during the following period of invasion, or the stage of toxemia, exactly corresponds with the spread of the virus through the body; it lasts three to five days and is characterized by chills, fever, backache and sometimes by a prodromal rash. Finally, the virus moves into the skin, bringing about the focal rash which is characteristic of the beginning of the period of eruption and the struggle in the skin. Secondary fever is associated with pustulation of the skin and by the absorption of the products of cell necrosis also in absence of secondary bacterial infections Now secondary bacterial invasion may be inhibited by antibiotic therapy.

The smallpox virus causes first a proliferative reaction (Wolman). Bras considered many cellular changes in smallpox as primarily degenerative in nature. It is probable that the first morphological changes created by the smallpox virus are proliferative followed by regressive alterations, i e. degeneration.

There are today only few opportunities of investigating cardiovascular involvement in smallpox in countries where vaccination is a routine procedure Dealing with cardiovascular involvement we have to rely on earlier work and the few recent authors who have recorded observations in their clinical and pathologic-anatomical material of variola. Former results are to be compared with recent investigations because (and this also applies to fatal cases) secondary bacterial complications are frequently avoided by antibiotic therapy. This treatment has the advantage that we may now more frequently have an unmixed and clearer picture of the smallpox virus infection although evolution and duration of the disease has been little changed by modern therapy.

Death in smallpox often occurs without a focal eruption and during the eruptive period. During the course of smallpox, the pulse becomes accelerated and the blood pressure lowered. Disturbances of the heart of varying intensity have been described. Death has been ascribed to heart

rash seen on earlier occasion was not German measles but another rash of a similar type, and that she wrongly supposed immunity.

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3. Variola

Variola (vera, Major) (smallpox) is an acute, highly contagious disease characterized by an initial period of fever, headache and backache, followed by a generalized typical rash which is first maculo-papular and later pustular with crust formation and with secondary fever at the time of pustulation. Variola minor (varioloid) represents an attenuated form and alastrim a mild form of variola. Vaccinia virus causes a mild disease in man. Cowpox virus closely resembles vaccinia virus immunologically and in host range. Variola virus differs from vaccinia in that its host range is limited to man and monkeys, and it cannot be propagated in series in ordinary laboratory animals. It can be grown readily in the chorioallantois of chick embryos. In this tissue it produces characteristic lesions different

subendocardial hemorrhages in the left ventricle have been occasionally observed in variola hemorrhagica Histologic findings are few although the clinical history is sometimes suggestive of myocardial damage. The most constant finding is a slight hyperemia in all vessels, and small hemorrhages are not uncommon in all types of variola. The subendocardial capillaries situated in the same layer as the conducting system of the heart, sometimes show stasis of large mononuclear cells and hyperplasia of the capillary endothelium At the same time a perivascular infiltration of lymphocytes, reticuloendothelial cells and some eosinophil granulocytes have been observed Sporadically, these perivascular infiltrations occurred around vessels in the subepicardial fat. No histologic changes in the myocardial fibres could be found through there was a slight interfibrillar edema In the necropsy cases of Bras all patients had received antibiotic treatment in a hospital, and this may account for the absence of streptococci which were seen, histologically, by previous investigators especially in purpura variolosa Therefore, in these cases secondary infections were much less important than is generally acknowledged, and in the majority neither bacteria nor reactive symptoms indicated their presence.

Wolman found, in a case of purpura variolosa, subepicardial hemorrhages, albuminoid degeneration of myocardial fibres and interstitial edema

On the basis of his 177 necropsies of smallpox cases, Bras concludes that there is a correlation between histologic changes in the subpapillary vessels of the skin and the tissues which they supply with blood, *i e.* in the overlying epidermis, juxta-dermal portion of the hairfollicles and sebaceous glands A similar correlation was found in other organs, it is likely that the damaging agent selects certain capillary groups and that an epithelial lesion or lesions in other organs appear only in areas vascularized by these capillaries According to Bras, purpura variolosa was not substantially different from variola vera, as it is advanced by some authors; these forms have the same basic pattern though part of it is different in development and/or intensity

The significance of capillary damage in vaccinia and variola infection was already stressed by Hassko who showed increased permeability of capillaries of internal organs in the vaccinia infection of rabbits

The variola virus has an affinity to the endothelial cells of many parts of the circulatory tree, especially in the skin. Wolman could demonstrate the migration of virus from the blood stream to the epithelial layer finding

failure and exhaustion, to toxic myocarditis, to pulmonary edema and just to exhaustion.

Anderson, Foulis, Grist and Landsman directed attention to the importance of cardiovascular damage in severe smallpox in the antibiotic age and gave a characteristic picture of their observation. According to these authors, a striking feature of five fatal cases was "myocarditis". Their patients were all young, of good physique, had no history of antecedent diseases and had little—if any—of the secondary fever as a result of antibiotic therapy. Nevertheless all five developed myocardial involvement, manifested by tachycardia, toneless apical sounds and irregular rhythm during their illness. Restlessness was not noticeable in any of these cases, but the patients, being nurses, were disinclined to ask for help for example in reaching for a sputum cup and exertion of this kind may have accentuated cardiac damage. They retained their lucidity of mind for a considerable time. They did not heed injunction to rest, and sedatives did not always ensure the desired relaxation. All five patients died from myocardial failure The authors thought it uncertain how much the toxemia resulting from extensive skin damage contributed to death; for myocarditis had already developed at an earlier stage. The nature of the cardiac damage was not known, but it may have been due to virus invasion. In view of the obvious cardiac damage, it was their impression that the utmost attention should be paid to the problem of how best to nurse smallpox patients in future epidemics so that such complications may be minimized Supportive measures—e.g. early blood transfusions, administration of Eucorton and vitamin K—may be advantageous especially in females, because hemorrhage and toxemia rapidly cause weakness which may be fatal

Earlier and recent opinion, indeed, prevail that myocardial involvement is responsible for the fatal outcome in smallpox which is not otherwise complicated and that, if the patient recovers, it is almost exclusively the heart that remains affected Those statements must be rescrutinized. Pathologists have recorded parenchymatous and fatty degeneration of the liver, the kidneys and the heart not only as remnants but also at early stages of the variola infection and some inflammatory changes in the myocardial interstitial tissue have been observed But Bras (1952) stressed that in smallpox the heart generally showed few abnormalities and its weight was nearly within normal limits Though he noticed subepicardial punctate hemorrhages, extensive hemorrhage was rarely seen. Small

circulatory failure and death. The recognition of the role of capillary alterations in smallpox may change the old conception of myocardial involvement in this disease. Myocarditis is not so frequently responsible for a fatal outcome of variola major as are the sequelae of capillary damage. More stress has to be laid on early therapeutic planning in case of vascular complications; this may save patients who until now perished from peripheral circulatory failure in this illness.

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4. Varicella

Varicella (chickenpox) is an acute contagious disease characterized by fever and an eruption of the skin and mucous membranes. It runs usually an uneventful course, but may occasionally assume the form of a severe disease showing manifestations not only in the skin and other epithelial surfaces but also in the lungs, the brain, the spinal cord and the kidneys. Chickenpox is capable of involving any epithelial surface and of causing systemic involvement. It appears that there may occasionally be an unusual susceptibility of the host to varicella virus.

The incubation period is about fourteen days. The first symptoms are shivering, fever, malaise, headache. The rash can be the first manifestation of illness and passes from a macule to a papule, to a vesicle which becomes pustular. There is a tendency of the skin lesions to appear in successive crops.

The virus is widely disseminated throughout the body. Although reports of necropsies in cases of varicella are scarce, those available indicate that the disease is a generalized one, affecting many organs and tissues in addition to the skin.

Small foci of necrosis occur in numerous organs, particularly in the lungs, the liver, spleen and adrenals. Thrombocytopenic purpura in varicella has been described. Hemorrhages related to the destruction of capillaries and to thromboses are noted. Inclusion bodies (type A) are found

inclusion bodies and extra-cellular virus aggregates within the endothelial lining of the blood vessels of various organs and mucous membranes.

Capillary damage in smallpox leads to increased permeability of capillaries, to the escape of protein and of oncotic chemicals into the tissues and, as a result of this leakage, to hemodynamic deficits. Heart failure in smallpox may be produced by the reduction of the active blood volume, decreased filling of the heart, reduced minute volume of blood. In overwhelming infections there is an additional loss of vasomotor and venomotor tone which hastens irreversible stasis and death. In not too severe cases, circulatory adaption to a lower blood volume is the rule. If there is recovery from smallpox, hypovolemia may still last for some period of time, until this decreased active blood volume is again normalized. According to Svertson and Hyman, the explanation of the cause of death in smallpox may lie in a profound physiologic disturbance from extensive skin destruction and transudation of fluids and electrolytes. The factors concerned require accurate analysis because there are metabolic disturbances apart from the circulatory deficiences in every severe smallpox case.

Smallpox may prove fatal before the appearance of any focal eruption, and the patient dies from "overwhelming hemorrhagic toxemia." On the other hand, smallpox may present a brief febrile illness devoid of localizing signs and neither accompanied nor succeeded by any rash (Marsden and Coughlan). Many cases are between these extremes and may be benefited by treatment. Some degree of control of the secondary bacterial illness and its complications may be derived from antibiotics. An important part of treatment is the early management of hypovolemia and of loss of vasomotor and venomotor tone Filling of the circulation is necessary in all cases who are not expecially mild and have to receive repeated and sufficient infusions of whole blood, plasma and blood substitutes (PVP, Periston, Periston N, Plasmosan, dextran). The myocardium will be adequately protected, and severe "myocardosis" can be avoided by this treatment. In peripheral circulatory failure the use of digitalis alone is valueless. Camphora, caffeine, cardiazol, coramine, and norepinephrine infusions are essential apart from blood plasma and plasma expanders for direct filling of circulation. The key to important parts of the pathological picture of smallpox is the severe capillary damage which leads to loss of plasma and electrolytes from the circulation, to hypovolemia, to loss of vasomotor and venomotor tone, to peripheral

especially in cases where antibiotic treatment prevents secondary bacterial complications.

Rosecan, Baumgarten and Charles (1952) described a case of varicella pneumonia and encephalitis associated with shock and heart failure. These authors reviewed the literature on chickenpox pneumonia during the antibiotic stage: Waring, Neubuerger and Geever (1942); Rausch, Grable and Musser (1943); Claudy (1942); Grayson and Bradley (1947); Bunn and Hammond (1950), Wesselhoeft and Pearson (1950); Frank (1950), Michel, Coleman and Kirby (1951), Eisenbud (1952). Rosecan, Baumgarten and Charles summarized the findings of 11 cases. In all cases reported there was a rapid onset of fever, dyspnea, tachypnea, tachycardia, cyanosis, cough, frequently bloody sputum within two to six days of the first appearance of the varicella rash Peripheral circulatory collapse occurred in three cases, two of them fatal. In several cases the symptoms of the pulmonary complications preceded physical symptoms by several hours especially when shock existed prior to the appearance of râles. Pleurisy occurred in four patients. Roentgenograms of the chest revealed nodular or miliary pulmonary infiltrations The densities were transient and disappeared after several weeks In severe cases there was a progressive retention of blood nitrogen In some cases hypalbuminemia was present. Waring, Neubuerger and Geever described an acute toxic encephalitis in a patient dying with chickenpox and pneumonia Three cases of pneumonia without associated shock and heart failure have been reported by Saslow, Prior and Wiseman.

We had the opportunity of observing three cases of chickenpox pneumonia, two men in 1947, one woman in 1952 The ages were 40, 36, and 20 respectively The course of the illness in three cases was almost identical. Three to four days after the onset of the chickenpox-rash, the fever rose again simultaneously with malaise, cough, bloody sputum, tachypnea tachycardia and hypotension The patients felt very ill The physical findings of the lungs were not pronounced; there were only some râles. X-ray examination of the chest in two cases, after three weeks, still showed residual basal infiltrations on both sides of the lungs. At the onset of the pulmonary complications leucocytes were 14,200, 12,300; and 7,000 respectively, and the serum albumin levels at the same time 2.8 Gm. per cent, 3 2 Gm per cent and 3 7 Gm. per cent respectively. All three patients developed varicella pneumonia in the course of penicillin treatment. A reduction of toxicity due to the absence of secondary bacterial infection may be possible. All three patients made a complete recovery.

in vascular endothelium and in lesions of organs, similar to those seen in the skin. These findings are in keeping with the hematogenous spread of the virus.

Hackel (1953) described the occurrence of myocardial lesions in association with varicella. There was 100 per cent incidence of myocarditis in seven patients who had varicella at the time of death. Six of the patients were children and one was an adult. In no case was myocarditis suspected clinically and in every case there were other conditions that seemed to be adequate as a cause of death. In all cases but one there was some bronchopneumonia or interstitial pneumonitis. In one case in which the clinical diagnosis of encephalitis was made, the necropsy finding was cerebral edema. Microscopic examinations of the hearts revealed scattered focal lesions in all cases. In four cases, these lesions were considered to be slight showing a moderate amount of interstitial edema and small focal collections of mononuclear cells, lymphocytes and occasional plasma cells, neutrophils and eosinophils. The infiltrates were often perivascular and extended for a short distance between the muscle fibers. The other three cases showed a moderate degree of myocarditis. Here the lesions were similar to those labelled as slight, but showed a greater degree of leucocytic infiltration The muscles were uninvolved for the most part, but occasionally showed evidence of necrosis, with globular swollen ends that were deeply eosinophilic without cross striations In none of the cases were inclusion bodies observed. A slight to moderate degree of epicarditis was present in all cases, but no evidence of heart failure was found in any of them. Postmortem cultures of the heart's blood were made in all cases but one and yielded no organisms Lung culture showed no growth in one case, Staphylococcus albus in one, in another there was a mixed flora including unidentified streptococci, in still another case Staphylococcus aureus and alpha streptococcus were found.

It was suggested that myocardial lesions might occur in non-fatal cases of chickenpox and could account for the frequent necropsy observation of focal myocardial fibrosis in patients with no history of previous rheumatic fever or other cardiac involvement.

Electrocardiographic alterations during and after varicella were observed by Waring, Neubuerger and Geever, Rosecan, Baumgarten and Charles; Betke and Harms and may be caused by myocarditis or by cor pulmonale or both. Cardiopulmonary manifestations in varicella sometimes present an opportunity for studying the pathogenesis of this illness

plies a similar pathogenesis. Increased pulmonary capillary permeability is present in all cases associated with the formation of hyaline membranes in the alveoli and may have the greatest importance for their origin. Different causative factors may lead to the same morphological picture (Weber). Bass, Greenberg, Singer and Miller stressed that the chief factor for the production of pulmonary lesions in their uremic patients was capillary damage and altered capillary permeability. In varicella pneumonia there are insults to the pulmonary capillary bed; the capillary permeability is increased and leads to subsequent transudation into the pulmonary tissues. The protein leakage into these tissues is a capillary syndrome, which may cause hypotension, hemodynamic deficits, peripheral circulatory collapse, shock and sometimes a fatal outcome. An associated hypalbuminemia was observed in the cases of Rosecan, Baumgarten and Charles; Grayson and Bradley and in my own cases; and may be an additional factor for the development of circulatory complications. In the case of Grayson and Bradley a perihilar density was suggestive of pulmonary edema

Treatment of varicella pneumonia with adequate doses of penicillin, streptomycin, or aureomycin is indicated in order to check secondary bacterial invaders Unfortunate results ensuing from the use of antibiotics as the sole treatment of severe pulmonary complications of chickenpox will sometimes occur Intravenous administration of whole blood, plasma, blood substitutes (Periston, Periston N, Plasmosan, dextran) are necessary to correct a decrease in the circulating blood volume. If this is delayed or is inadequate, irreversible shock may develop. Profound anoxia and severe hypodynamic circulation cannot sometimes be corrected.

Rosecan, Baumgarten and Charles emphasized that the dramatic improvement in their case followed the administration of digitalis. When symptoms and signs of acute cor pulmonale appear, intravenous infusions should be discontinued. The cardio-pulmonary balance, in such cases, requires careful judgment because a big amount of intravenous fluids may produce pulmonary edema Oxygen may be required. Rapid digitalization as well as other measures used in the treatment of acute heart failure are necessary.

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Waring, Neubuerger and Geever; Claudy; Frank; and Hackel described the histologic findings of varicella pneumonia or pneumonitis. Generally multiple, fairly large foci of fibrinous exudation filled the alveoli. The alveolar walls were lined with hyaline membranes in many areas. The alveolar cellular exudate was chiefly mononuclear. Macrophages were present in large numbers within the alveoli. The septal cells were moderately swollen and hyperplastic and often appeared as a continuous layer of cells lining the alveoli. Numerous areas of necrosis were distributed throughout the lungs. Alveolar cells were necrotic, and the arteries in these areas were also involved in the necrotic process. The bronchioles showed severe desquamation of the lining epithelium. Many large, rounded, well-defined inclusion bodies were seen by Frank within the desquamated septal cells and in an occasional non-desquamated septal cell and bronchiolar epithelial cell. No inclusion bodies were observed in any of Hackel's lung sections.

According to Frank, the general picture is that of patchy bronchopneumonia with areas of consolidation and a tendency toward confluence without suppuration. Except for the characteristic intranuclear inclusion bodies, none of the changes are peculiar to varicella pneumonia. They have all been found in other types of virus pneumonia, influenzal pneumonia, in acute rheumatic fever and in radiation-pneumonitis.

In the cases of Rosecan, Baumgarten and Charles, varicella was associated with pneumonia and encephalitis, the initial and critical complication was the profound and prolonged shock with fever and anoxia. The chief manifestation was extensive pneumonia lasting for more than six weeks and finally dissolving. Rosecan, Baumgarten and Charles assumed that the shock was presumably due to viremia itself or to the toxic reaction to extensive viral infection. The demonstration of varicella inclusion bodies in vascular endothelium suggests widespread vascular damage due directly to virus. Heart failure in this case occurred as a result of acute cor pulmonale or, perhaps, additional myocardial damage.

Recently Bass, Greenberg, Singer and Miller reported on a series of uremic lungs; these changes are non-specific, and the pathologic features are very similar to those seen in varicella pneumonia The alveolar spaces were filled by plugs of round hyaline bodies. These findings explain the profound dyspnea from which these patients suffered and suggest that the cause of death in such patients was anoxic rather than of renal origin.

The resemblance of abnormal pulmonary findings in many conditions im-

the lesions probably result from a hematogenous spread in a non-immune individual while in herpes zoster they are tentatively considered to result from a neurogenous spread in a person with *humoral immunity*.

A hypothesis of Stokes considers the varicella virus as infecting the general population almost universally at an early age. A generalized infection with the virus with a relatively long incubation period may permit the development of permanent resistance. However, in certain cases the varicella virus may have neurotropic properties as indicated by the simultaneous development at times of zoster and varicella, and it may remain within the nerve cells of a few individuals in a manner similar to the symbiosis exhibited by herpes-simplex virus and ectodermal cells. In adult life exposure to cold, pressure on a nerve or a fresh massive dose of varicella virus may cause a localized virus activity along posterior root fibres with subsequent development of zoster vesicles According to Burnet varicella is a trivial disease, but the evident relationship to herpes zoster poses a whole series of problems. Many questions arise: How does virus circulating in the blood reach the site appropriate to its multiplication? Is the capillary endothelium of each organ in some way related to its characteristic cell so that infection of endothelium as well as of parenchymatous cell can occur? There is the standard problem of the transport of virus by nerve paths also Feyrter considers zoster as a disease provided by hematogenous spread of virus

It has been assumed that "herpes zoster" virus may remain latent in the body's tissues for a prolonged time and become active in association with diseases of the spinal cord and column, leukemia or some other disturbance of the host's body

Herpes zoster is associated with unilateral inflammation of posterior root ganglions, posterior nerve roots, peripheral nerves or extra-medullary ganglions or cranial nerves Neural inflammation is accompanied by marked pain followed by the eruption, in areas supplied by sensory nerves

Histologic changes of herpes zoster are vascular congestion, hemorrhages, necrosis, perivascular collections of lymphocytes and degeneration of ganglion cells The process is patchy and a smaller or greater part of cells escape without damage There may be a localized process in the posterior horns of some segments and occasionally, in the anterior horns with subsequent degeneration of motor nerve fibres and muscles. Congestion in spinal meninges is frequent though encephalitis is rare. The disease is rare in children, frequent in middle aged and old people.

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5. Herpes zoster

Herpes zoster (zoster, shingles) is an inflammatory disease characterized by neuralgia and by an eruption which runs unilaterally around the body. The eruption is first an erythema, then papular, then vesicular. The vesicles contain a fluid, at first clear but later purulent. These vesicles break and form crusts. Inclusion bodies demonstrated in cutaneous lesions and elsewhere, indicate the viral etiology of herpes zoster. The virus is closely related to the virus of varicella. Rhodes and van Rooyen assume that chickenpox and zoster virus strains share antigenic components and are members of the same group of viruses but are not identical Many others considered the causative agent of varicella and herpes zoster as the same thing. Brain thought that the sensory neuron had a tissue immunity feebler than that of other parts of the body, or that its immunity might be temporarily diminished by preceding damage so that an infective dose in the adult life tended to produce herpes zoster.

According to Findlay, varicella is a disease of the young, zoster of the more mature. The fact that resistance increases with age against subcutaneous or intraperitoneal injection, but not against inoculation directly into the nervous system, may explain the relative age incidence of varicella and zoster. In the young the virus produces a generalized infection which immunizes all the tissues of the body except those of the nervous system; in the mature who have had varicella, direct contact of zoster virus with nervous tissues, as, for instance, the endings of the olfactory nerve, may produce a disease restricted to nerve tissue According to Cheatham (who also considered the zoster and chickenpox viruses as identical) in varicella

have received "after the occurrence of herpes zoster at the portal of entry but before the outbreak of the rash." Cardiac alterations in this case were attributed to nitrogen mustard therapy.

A case of cervicothoracic herpes zoster has been reported which was followed after seven days by endocarditis (Andreassian, 1934).

Gais and Abramson found, in four cases of herpes zoster, precordial pain radiating down the left arm which was accompanied by dyspnea and alterations in the cardiac rhythm.

Cardiovascular disturbances could not be detected in any of my 23 cases examined from 1952 to 1954. Radiating pain in the left or right arm, tingling in the fingers are not rare in herpes zoster but not necessarily a sign of cardiovascular involvement. Even in cases of old people with coronary heart disease, herpes zoster did not alter electrocardiographic abnormalities seen prior to the onset of zoster. In four patients suffering from severe postherpetic neuralgia for weeks or months, cardiovascular disturbances and electrocardiographic alterations could not be observed. Only one patient, 73 years old, suffering from persistent neuralgia, developed a myocardial infarction following zoster.

Herpes zoster may occasionally simulate intra-abdominal or heart disease Confusion mainly occurs in the pre-eruptive stage.

Zoster of the third and fourth posterior roots may cause paralysis of the phrenic nerve on the same side associated with dyspnea on exertion and on bending over (Halpern and Covner). I saw a 40 year old woman with herpes zoster involving some unilateral thoracic segments. On the eighth day of the illness, the patient developed severe pain in the upper abdomen which quickly increased, vague digestive complaints and loss of appetite. The temperature was normal The abdomen showed considerable tenderness, the patient had vomit, shock with a pulse of about 140 and drop in blood pressure A laparotomy revealed thrombosis of superior mesenteric veins and, on the left hypochondrium, a convolution of gangrenous intestinal loops. The involved portions of the intestine were resected but the patient died on the same day

Feyrter recently added a concept of great importance to the knowledge of zoster The author assumes that the disease results from hematogenous spread of virus and on the other hand, there is evidence pointing to the fact, that the patient presents at the same time signs of vascular hypersensitivity.

Feyrter found capillaritis, arteritis of the periarteritis nodosa type, and

The question as to the portal of entry and routes of infection has been frequently discussed. It is assumed that the skin eruption is produced by primary involvement of the spinal or other ganglia but how the virus reaches the ganglia has not been ascertained. After an incubation of seven to fourteen days during the prodromal phase of herpes zoster, respiratory and digestive disturbances may occur and are probably indicative of the portal of entry of the virus which may reach the blood stream and cause a short viremia. In 1900 Haslund noted that herpes zoster was often ushered in by upper respiratory symptoms, sore throat, angina; he regarded the tonsils as the probable portal of entry. Thereafter, the virus is carried by the blood stream to one or more posterior root ganglia and thence, via a sensory nerve, to the skin. There may be a hematogenous or a neurogenous spread of virus.

Dahl regarded herpes zoster as a viral infection that enters through the alimentary tract producing a viremia. He recorded a case of a patient who was one month pregnant when suffering from the disease and whose child was born with a harelip, cleft palate and atresia of trachea.

Cheatham demonstrated intranuclear inclusion bodies within the esophageal mucosa, mesenteric plexus of the stomach, dorsal root ganglion and a sympathetic ganglion at the level of the affected dorsal root ganglia. Similar inclusion bodies were observed within cells in lesions of the pancreas, adrenals, one ovary, associated with focal necrosis. Cheatham suggested that the virus might enter the body via the sympathetic nerves of the esophagus and migrate by the sympathetic nerves to the dorsal root ganglia, eventually reaching the skin by centrifugal spread along the respective peripheral nerves. Inclusion bodies are described in the endothelial cells of vessels of the skin lesions. Virus must be liberated into the blood with death of infected cells; if there were no humoral immunity in zoster, the lesions would generally be widely disseminated. Varicelliform lesions may occur in the course of a zoster infection when generalized immunity has been lost and hematogenous spread of virus occurs.

Cardiovascular involvement has not been described by pathologists. Only Cheatham found, in his case of herpes zoster with varicelliform eruption, multiple foci of myocardial necrosis with associated hemorrhage in the myocardium, endocardium and epicardium. It was assumed that the patient was suffering from Hodgkin's disease but it was impossible to confirm the diagnosis from necropsy findings. Death of the patient may be attributed largely to nitrogen mustard therapy which the patient must

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6. Herpes Simplex

Herpes simplex is a very frequent chronic infection of man. It usually appears on the lips, occasionally on the skin and rarely on the cornea or genitalia. Clinically, the infection presents itself in the form of stomatitis, herpes febrilis, herpes simplex, herpes cornealis, recurrent herpes, disseminated herpes simplex (eczema herpeticum, Kaposi's generalized varicelliform eczema), encephalitis, encephalomyelitis and meningoencephalitis.

The primary infection usually appears in infancy or early childhood as aphthous stomatitis and persists through life generally remaining quiescent. Appropriate stimuli will excite herpes in regions where it normally lies latent and leads to shedding of infective virus. The damaged skin is an ideal site for chance inoculation of herpes virus.

Primary herpetic infection of the adult very rarely occurs. Antibodies are present in the serum of most older children and of adults but are not found in infants or younger children. Antibody formation develops following a primary infection and persists for life. The herpes infection usually is inapparent and its occurrence can therefore be recognized only by the presence of circulating antibodies. However, according to Rogers, Coriell, Blank and Scott, in about 1 per cent of all infections the first attack of the herpes virus can give rise to a serious or even fatal disease.

The virus of the disease may be present in the vesicle of herpes and may be found in the blood of persons suffering from herpetic eruptions and, occasionally, in the cerebrospinal fluid and saliva of patients.

Type A intranuclear bodies, known as Lipschuetz bodies, are present in herpes simplex, they are found in epithelial cells of the primary lesions and in nerve cells and glia when these are reached and infected by the virus.

In human herpetic meningoencephalitis, the chief sites of the changes

phlebitis with and without hemorrhage, and with and without necrosis which he termed periarteritis nodosa zosterica. In the common periarteritis nodosa neuritic pains are frequent and are dependent on lesions of peripheral nerves. In zoster there is an inflammatory condition of the nervous system which often affects posterior root ganglia. We have already mentioned the observation of thrombosis of mesenteric vessels in a case of zoster.

Mesenteric vascular disease occurs in periarteritis nodosa. According to Feyrter an angitic diathesis may be present in individuals suffering from zoster and many organs may be involved in this disease.

In two of his cases of arteritis zosterica, death was due to zoster. It may be possible that cases of zoster which recover may occasionally develop late symptoms of renal vascular or cardiac disease. It is also possible that zoster may be associated merely with transient capillary damage (capillaritis zosterica) and that alterations of internal organs occurring in zoster may be frequently transient and of short duration like the changes of the skin which may not be found later or may be demonstrated at autopsy (Cheatham, Feyrter).

The conception of vascular hypersensitivity playing a role in zoster may be important for the treatment of the disease. Arteritis zosteric and periarteritis nodosa are regarded as "hyperergic" inflammation of the vessels. When treated early with cortison, encouraging response in periarteritis has been observed. Harvey, Howard, and Kathis, Gelfand, Poulin, Weinstein and Lamas have noted a favorable response in patients with severe herpes zoster treated with cortisone or cortitropin (ACTH). This therapy should be reserved for patients in the older age group and for those failing to respond to conventional methods.

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little doubt that a hematogenous spread is primarily responsible for an atypical form of disseminated herpes that has been reported by Zuelzer and Stulberg and by Pugh, Newns and Dudgeon. The virus of herpes simplex can cause a fatal disease in the newborn in the absence of significant cutaneous lesions and can invade the blood stream during herpetic gingivostomatitis in older infants, giving rise to specific herpetic hepatitis. Fatal cases of hepatic necrosis in disseminated herpes simplex were described by Hass; Quilligan and Wilson; Zuelzer and Stulberg; Pugh, Newns and Dudgeon, and other authors (1954, 1955).

Most investigators emphasized that herpes simplex virus progresses along or within axis cylinders. A neurotropic strain of herpes invades the central nervous system through the nerves from the inoculated parts; lesions make their first appearance in the segments with which such nerves are associated. Some authors are inclined to the belief that the invading virus of the central nervous system passes in endoneural (lymphatic) spaces and in vascular adventitial space of the nerves. These points have never been finally settled. Field's experiments of masseteric inoculation with herpetic material tends to support the hypothesis of lymphatic space progression rather than axonic transmission; the possibility of a blood-borne infection has also been considered. After masseteric injection, when islands of infiltration are found in the muscle, and after corneal scarification, there must be considerable nervous irritation. There are indications that, as a result of peripheral nervous irritation, the blood-brain barrier in the corresponding nerve-root region may be lowered. If small quantities of virus happen to be circulating in the blood at the time when localized vascular permeability develops, a settling-out might result. Marinesco and Draganesco (1932) found a wedge-shaped lesion in the spinal tract, analogous to that following corneal inoculation in two cases in which the masseter has been injected and in one, following inoculation of the vagus nerve They believe that some vascular factor may determine the localization (quoted by Field). Van Rooyen and Rhodes say, "Whether the virus spreads by the axis cylinders or by perineural lymphatics is not known, but nerves are evidently the important pathway of infection Blood spread may, however, play some part . . ." Further studies of the vascular changes in the medulla following corneal inoculation of herpes are in progress (Field). The herpes is considered a virus with dermatotropic and neurotropic properties. The dermatotropic affinity is indicated by the infection of the skin and the cornea; the

are the cortical and subcortical white matter. There are softened areas of necrotic cortex. In the neighborhood of the necrotic areas there is an increase of glial cells, many of which (as well as some neurons) contain inclusion bodies. There is a mononuclear infiltration of the leptomeninges in the vicinity of the areas of encephalomalacia (Smith, Lennett and Reames; Zarafonetis, Smadel, Adams and Haymaker; Wildi). Such areas of softening with loss of architecture and with intranuclear inclusion bodies are considered characteristic of herpetic encephalitis (Whitman, Wall and Warren). France and Wilmers reported herpes simplex and encephalitis in newborn twins.

Histological changes occurring in herpes infected chick embryos have been described by Anderson. This author showed that the virus could spread from the original point of inoculation by three ways: 1) by invasion of the intact epithelium and spread by continuity of infection, 2) by hematogenous transmission of the virus to establish a general infection. Inclusion bodies were found in the endothelium of larger vessels and capillaries. On successive membranal passage the virus produced more severe lesions in the endothelium and mesoderm such as cardiac muscle and liver; inclusion bodies occur in these sites and also in interstitial tissues. 3) by both centripetal and centrifugal neural transmission of infection. An increase in the virulence of the virus for chick embryos is expressed by an enhancement of its ability to infect mesodermal and endodermal structures.

Slavin and Berry using suckling mice found disseminated blood-borne lesions in the liver, adrenals and bone marrow regardless of whether the intranasal or peritoneal route was used for inoculation of herpes virus.

A certain proportion of rabbits inoculated upon the cornea with herpes simplex virus developed fatal encephalitis (ceratogenic encephalitis). Since Doerr and Voechting were able to produce the same condition by intravenous injection of herpetic material they concluded that brain infection following corneal inoculation took place through the blood stream. Levaditi and many others express the opinion that in all probability there is a transitory appearance of herpes virus in the blood during the acute stage of the disease. According to Barrow the primary inoculation of herpes virus may be via the damaged skin. Subsequent dissemination is hematogenous with localization in damaged areas.

According to Slavin the development of Kaposi's herpetiform eruption would seem to depend on the hematogenous spread of virus. There seems

of infancy. The essential features of herpetic lesions in the internal organs are necrosis and typical intranuclear inclusion bodies (Zuelzer and Stulberg; Pugh, Newns and Dudgeon; *and other authors*).

Cases of herpes simplex infection of infancy may have been described under the term "salivary gland virus *disease*," "*inclusion* disease" or "cytomegalic inclusion disease" since the histopathology of both infections is very similar, even identical; and laboratory *diagnosis of herpes* simplex has often been omitted. In cytomegalic inclusion disease, interstitial myocarditis has already been reported, but in herpes simp*lex it has* not been observed. Pugh, Newns and Dudgeon mentioned in connection with their case of hepatic necrosis in disseminated herpes simplex, *that* the myocardium was paler than normal and showed cloudy swelling and edema.

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neurotropism is shown by the experimental and human encephaliti: But according to Seiffert the herpes simplex virus is to be regarded a pantropic since it can evoke alterations in all the three germinal layers

Cardiovascular involvement has scarcely been seen in human herpe simplex infection. We observed a severe herpes encephalitis following primary herpes simplex over the left knee region in a woman, 28 years o age. There was fever which returned to normal levels by lysis during th first seven days of illness. The patient was suffering from severe head ache, nervousness, disturbed sleep. Her speech was slow and incoherent There was transient dimness of vision, transient pupillary changes, bu normal discs. Alterations of reflexes, abnormalities of taste and smell were present. The development of an increasing titer of circulating antibodies against herpes simplex was found. The encephalitis lasted for three months and was followed by a long period of neurocirculatory asthenia. An explanation of this circulatory asthenia cannot be offered. It may be attributed to injury of the vasomotor centers in the brain or to extensive involvement of the brain. A myocardial injury is improbable; the electrocardiograms were always normal.

In the clinical picture of herpes simplex as the cause of fulminating visceral disease of the newborn, according to Zuelzer and Stulberg lesions of the conjunctivae and skin arouse a high degree of suspicion. Otherwise the cases are remarkably similar, with the onset of the systemic reaction about the fifth to seventh day of life, fever or hypothermia, increasing icterus, lethargy, respiratory distress, vomiting, dyspnea, cyanosis, and the rapid development of a state of circulatory collapse Enlargement of the liver and sometimes the spleen complete the similarity of this picture to that of bacterial sepsis which will always be thought of when skin or mucous membrane lesions suggest a portal of entry for bacteria Such lesions are equally well suited to the entry of herpes virus. But surface lesions may be absent or so inconspicuous that a clinical diagnosis of herpes does not suggest itself even in retrospect Visceral lesions attributable to the herpes virus are much more limited in distribution and, on the whole, much less severe in older than in new infants

But the occurrence of herpetic hepatitis with fatal outcome directly attributable to the disease raises the problem of the frequency of viremia and of visceral lesions in primary herpetic infections not only of infants but also of older children and adults. In any event, viremia is probably a frequent, if not a *regular* phenomenon during primary herpetic infections

The disease is diagnosed, according to Rivers, by the knowledge of exposure to the virus in the laboratory or to the infected poultry, by isolation of the virus from the conjunctival exudate and its identification by means of the hemagglutination inhibition test and by determination of the development of specific neutralizing antibody by test on paired sera collected from patients during the acute and convalescent stages of the disease.

Newcastle disease virus resembles influenza virus in its ability to grow in fertile eggs, in the production of thick red cell or other red cell-hemagglutination. Despite similar biological properties, serological tests show no antigenic relationship between the viruses of influenza and Newcastle disease. Moolten and Clark reported a case in which the virus of Newcastle disease was isolated from the blood of a woman shortly after subsidence of acute hemolytic anemia with autohemagglutinative vascular phenomena. During the active stage of the disease the patient had an eruption resembling that of acute disseminated lupus erythematosus.

Moolten, Clark, Glaser, Katz and Miller reported blood stream invasion by Newcastle disease virus associated with hemolytic anemia and encephalopathia. It is suggested that the virus may circulate in the blood, be adsorbed to erythrocytes causing hemolytic anemia, intermittent intravascular hemagglutination and, in vitro, autoagglutination of red cells. Perhaps such infections are usually latent but become provoked by non-specific stimuli or reduction in non-specific resistance. There may be a possibility that Newcastle virus is a hemotoxic agent in humans and may be the cause of an acute hemolytic anemica but further studies will be necessary to define its practical clinical significance.

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2. Behçet's Disease

Behçet's disease is a relatively rare disease showing three basic and invariable signs common to all cases: recurrent irridocyclitis, aphthae in the mucosa of the mouth and superficial genital ulcers. According to

CHAPTER IV

Diseases of the Eye

INVOLVEMENT of the eyes occurs in a series of viral infections. Smallpox, measles, herpes simplex, herpes zoster and infectious mononucleosis can affect the eyes. Lymphopathia venereum may produce various ocular conditions. Cat-scratch disease may be the cause of Parinaud's oculo-glandular syndrome in which the conjunctiva is the site of the primary infection followed by regional lymphadenitis. The ocular manifestations of infectious mononucleosis may be divided into two groups:

1) Those possibly due to direct involvement of the eye and its adnexes by the characteristic pathologic lesion of infectious mononucleosis.

2) Those affecting vision and the neuro-ophthalmologic apparatus owing to a more remote occurrence of the lesion most commonly involving the central nervous system (Tanner).

Trachoma and inclusion conjunctivitis are viral infections of the external eye. The virus of inclusion conjunctivitis may cause urethritis and cervicitis. Also, epidemic keratoconjunctivitis (virus-keratitis, keratitis-punctata, superficial-keratitis) is caused by viral agents. Newcastle disease and Behçet's disease are viral infections of the eyes.

1. NEWCASTLE DISEASE

Newcastle disease breaks out in epizootics (animal epidemics). It affects primarily birds and is characterised by viremia, signs of involvement of respiratory, gastro-intestinal and central nervous system (avian pneumoencephalitis). Most animals are highly resistant to potent laboratory strains of the virus, man is rarely infected. In man the virus causes unilateral, superficial conjunctivitis without involvement of the cornea and with pre-auricular lymphadenitis. There may be headache, discomfort and chills, an influenzal type of illness It may produce rhinitis, pharyngitis and bronchitis (Siegert, Haussmann and Mannweiler). It may cause poliomyelitis-like symptoms in children or, perhaps, pneumonitis in adults. But the ocular manifestations are the established instances of human Newcastle disease. The illness is of short duration and usually without sequelae. No signs of cardiovascular involvement have been described in acute human cases. The disease mainly occurs in people who work in laboratories or otherwise handle infected birds.

kidney and liver, bronchopneumonia and pulmonal edema The findings in the posterior segment of the eyeball—with the optic nerve attacked—presented scattered perivascular round cell infiltration and cell invasion around the central retinal artery and its retinal branches, in the chorioid and the sheaths of the optic nerve. Silfverskioeld observed, at autopsy, encephalomyelitis with softened and necrotic areas in the peduncles, the bulb and the upper part of the spinal cord.

Perivascular cellular infiltrations may develop not only in the eyes but also in the brain, kidney, liver and other organs. Generalized vascular damage seems to be possible in Behçet's disease. Curth thought that the manifestations of the central nervous system may be perhaps explained by disturbances which begin as vascular lesions most probably in the veins. This is also the opinion of France, Buchanan, Wilson and Sheldon. In some cases cardiac valve disease has been reported, but these conditions may result from other causes and in one case of Feigenbaum and Kornblueth the presence of endocarditis was suggested but the diagnosis appears not to be clearly established. Thrombophlebitis was reported in more than 25 per cent of cases Attacks in some instances were multiple.

Lemke stressed the frequency of vascular alterations in Behçet's disease and mentioned affections of the vessels of the uveal tractus, the central nervous system, hemorrhages into the skin and mucous membranes, thrombophlebitis, hemoptyses, myocardial damage and coronary insufficiency More attention should be paid to the possible cardiovascular involvement in Behçet's disease, especially in the usual chronic and recurrent cases Behçet's disease must be added to the list of infections produced by neurotropic viruses. Treatment with cortisone and corticotropine was tried, some results were disappointing (France, Buchanan, Wilson and Sheldon), but recent authors reported more satisfactory and encouraging effects

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Feigenbaum and Kornblueth, Behçet's syndrome needs a correction insofar as the ocular symptoms comprise not only uveitis but also neuroretinitis. On the basis of the studies of 32 cases, Behçet concluded that the ocular lesions actually begin in the retina and optic nerve and the uveal disease manifests itself later. Both eyes were always affected simultaneously or the one after the other. In addition to the three major manifestations other signs and symptoms may accompany the disease. Possible associations are phlebitis, encephalo-myelitis and -meningitis, anemia, headache, and orchitis. Encephalitis cases are reported by Knapp, Berlin, Alm and Oeberg; Silfverskioeld, Thomas, Curth, Alma and Magni; and Herrmann. Ocular and other manifestations are recurrent. There is no doubt that Behçet's disease is a generalized disease and not a series of local pathological processes unconnected with one another. The gravity of the disease is demonstrated by the frequent fatal outcome.

Behçet proposed that the disease was caused by a special virus, although he was unable to demonstrate one. The results of his histopathologic and bacteriologic investigations of the aphtous lesions and of his experiments on animals were consistently negative, but he insisted that he observed inclusion-like forms in smears from the hypopyon of the anterior chamber and from the aphtae.

Alm and Oeberg were able to produce retinitis, uveitis with hypopion, and meningoencephalitis in rabbits through four generations. A viral origin was also assumed by Katzenellenbogen, Silfverskioeld and Sezer.

Sezer isolated a virus from each of three patients with Behçet's disease. In each instance the virus displayed the same cultural and serologic properties. It caused typical encephalitis in mice and produced in the eyes of rabbits a disease similar to the disease in man Positive complement fixation and neutralization tests indicated that special antibodies against this virus are being produced in the blood of patients with the disease. The virus multiplied in the chorioallantoic membrane of a fertile egg, and in the yolk sac, and caused the death of the embryo in a high percentage of experiments. The virus killed guinea pigs by causing hemorrhagic lobar pneumonia. The virus passed through a Seitz filter with double pads. The diameter of the virus particles is about 100 millimicrons

Fatal cases of Behçet's disease showed meningitis, multiple necrotic areas and diffuse perivascular round cell infiltration in the brain and the spinal cord. Berlin found diffuse perivascular round cell infiltration in the

kidney and liver, bronchopneumonia and pulmonal edema. The findings in the posterior segment of the eyeball—with the optic nerve attacked—presented scattered perivascular round cell infiltration and cell invasion around the central retinal artery and its retinal branches, in the chorioid and the sheaths of the optic nerve Silfverskioeld observed, at autopsy, encephalomyelitis with softened and necrotic areas in the peduncles, the bulb and the upper part of the spinal cord.

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CHAPTER V

Respiratory Diseases

1. Influenza

Influenza is an acute infectious disease of man which is caused by viruses of the influenza group. The illness is characterized by fever, prostration and an affection of the respiratory tract. Influenza alone can produce pneumonia but there is often a tendency to secondary pulmonary infections. Influenza occurs epidemically and sporadically. Variations of the influenza viruses overcome the host's immunity. Influenza viruses are unequalled by most other viruses in their notorious variability.

Although the disease is caused by either influenza A or influenza B strains, which are antigenetically separate, or by both at once, major epidemic outbreaks are attributed chiefly to virus A strains. Virus C is only rarely found, has not been observed in any major epidemic and causes milder symptoms than A or B.

It has been suggested that there should be in influenza, a continuous selection of antigenic variants The viruses undergo successive antigenetic changes from one epidemic to the next. Individual members of an influenza virus strain may be prevalent one time and then decrease and disappear while new members take their place. Others think that influenza viruses contain a number of antigenic components which undergo quantitative changes or re-arrangements within the virus particles from one epidemic to another Every influenza epidemic now appears to be pandemic. Prevalent virus strains though widely separated in areas are at the same time relatively homogeneous While the antigenic analysis has, to some extent, elucidated the geographic pattern of the epidemic spread of influenza during the last years, it has thrown no light on other features. There exists the possibility that some environmental features may determine the local course of an outbreak but there may also be biological characteristics of the causative virus which are not reflected in its antigenic construction (Smith, Westwood and Belyavin)

In influenzal disease, there is an incubation period of a few hours or up to 48 after which the patient suddenly gets ill with shivering, lassitude, prostration, aching of the head, back and limbs, rise of temperature

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generally characterized by an inclination to circulatory failure (Belloni, Gottheil, Hart, Hubert, Kahlstorf, MacKenzie). On the other hand in some texts of internal medicine and cardiology no mention is made of influenza as a causative factor in cardiovascular disorders. Influenza myocarditis has been described by the older generation of clinicians, note Leichtenstern (1896) Wuhrmann in 1939 considerably deepened our knowledge of influenzal myocarditis by a monograph of outstanding importance Finland, Parker, Barnes and Joliffe discussed the relation of the influenzal virus to cardiac damage and were the first to suggest that cardiac lesions are the result of infection with influenza A virus. It has been maintained that circulatory failure in influenza should be due to general vasomotor paralysis Wuhrmann pointed out that a distinction should be made between myocarditis and a functional circulatory failure in influenza. According to Bramwell and King, neurocirculatory damage often follows influenza. In White's opinion, the weakness and cardiovascular symptoms that so often follow severe influenza and may persist for weeks or even for months, should be ascribed to a marked neurocirculatory asthenia caused by this particularly exhausting disease rather than to involvement of the heart itself

Christian described a vasomotor imbalance sometimes occurring in early convalescence It is not easy to evaluate the relations between influenza and cardiovascular symptoms and signs Cardiac and extracardiac factors in the development of cardiovascular disturbances should be distinguished There is much reluctance to acknowledge the connection between influenza and cardiovascular disease because similarity of many clinical entities makes an accurate influenza diagnosis solely on the basis of symptomatology very difficult Lack of knowledge as to the causative agent in many cases should not, according to Wuhrmann, make us neglect or underestimate the manifold irrefutable clinical observations. Today the diagnosis of influenza disease can be directly achieved in the early stage by recovering the virus from the nose or throat of the patient; in fatal cases it may be obtained *from the lung* *A certain* diagnosis can be obtained by complement fixation or neutralization tests for antibodies provided that serum can be examined from the patient early in the infection and again on about the twentieth day of illness.

For many complications of influenza, secondary bacterial invasion seems to be the rule Influenzal pneumonia has a particular predilection for Staphylococcus aureus and its presence further suggests the diagnosis of

to 103°, and frequent pulse. A few moist râles appear over the lower lobes, posteriorly, or some scattered rhonchi may show. The temperature returns to normal about the third to fifth day, and recovery follows. A number of cases develop bronchitis and bronchopneumonia. The temperature is between 100 and 104°, the pulse may be rapid. The patient is cyanotic. Cough is troublesome, the sputum often contains blood. Examinations of the lungs show rhonchi, râles, weak breath sounds and areas of dullness

According to Mulder and Stuart, two main varieties of complications of the lower respiratory tract are frequently observed—influenzal bronchitis and bronchiolitis—and influenzal pneumonia. The danger of influenza appears to lie largely in the pulmonary implications associated with this disease. On the other hand, influenza virus A infections occur with benign pulmonary infiltrations, in which also no myocardial or hypotensive involvement has been demonstrated (Scher and Jaruczewski).

There are large numbers of deaths reported as due to influenza and especially among people over fifty-five. No other disease affects such a high number of the population and causes such a sharp rise in the death rate.

In Burnet's opinion, influenza viruses A and B are pneumotropic; they invade and multiply in cells lining the upper and lower respiratory passages. The influenza virus establishes a focus of infection somewhere in the respiratory tract in a typical attack. "Here an epithelial cell is invaded and the virus multiplies causing necrosis and liberation of virus in the epithelial surface Further cells are infected, and the process continues sweeping over the epithelial surface like a prairie fire" (Burnet). The pandemic virus of 1918/19 was probably similar antigenetically to influenza virus A but possessed the biological property of attacking the alveoli as distinct from the bronchi and perhaps of affecting vascular endothelium also (Burnet and Clark). According to Mulder and Stuart, the potentially pneumotropic property of influenza cannot be ignored and some strains of influenza may multiply more readily in the human lung.

A relationship between involvement of the cardiovascular system and influenza has been known for a long time. Some authors are of the opinion that it is a more or less frequent cause of cardiovascular disturbance It has been maintained that no other disease—even in non-fatal cases—is likely to produce so much damage to the heart, and that this infection is

tion, edema of alveolar walls and infiltration of monocytes. There was swelling of the cells lining the alveoli. In the second case of uncomplicated pneumonia there was dilatation of ductuli alveolares and the alveolar walls were lined with dense hyaline membranes. Desquamation of epithelium was limited to the alveoli. Such hyaline membranes resemble the membranes which have been observed in fatal cases during the 1918 epidemic (Goodpasture, LeCount, MacCallum, Wolbach).

The influenzal pneumonia may be considered as a result of severe capillary damage, subsequent increased permeability of capillaries and leakage of protein and electrolytes into the tissues. According to Barden and Cooper, there may be a rapidly spreading hemorrhagic pneumonia. Blood leaks into the alveolar septa. The patients exhibit signs and symptoms of a rapid pulmonary failure which seems to be out of proportion to the roentgen changes in the chest. Sometimes an increasing haze may envelop the lungs from the periphery toward the hilus becoming dense and confluent from hour to hour until no aerated lung remains visible. These changes are not specific and are found in other conditions brought about by altered pulmonary permeability. Not too severe cases also show evident oxygen want and positive pressure oxygen may bring about relief and recession of the condition. The capillary syndrome in influenza is associated with hemodynamic deficiencies (hypotension, decreased circulatory blood volume) and may lead to peripheral collapse, shock and, not too rarely, to death Pulmonary vascular changes in influenza caused by capillary damage and their sequelae occur more frequently than is generally recognized Early administration of whole blood, plasma and plasma substitutes plus norepinephrine may be life saving.

In two cases of acute myocarditis described by Finland et al. influenza A virus was the cause of direct cardiac involvement. One of these patients died of cardiac failure and had a minimum of pulmonary involvement. The other died of an extensive acute bronchopneumonia from which no significant bacterial pathogen could be recovered Influenza A was isolated from the lungs of both cases. The autopsy in the first case revealed an extensive myocarditis with necrosis of occasional muscle fibres, in addition there was a moderate cellular infiltration of the interstitial tissue. The myocarditis of the first patient was of approximately two to four weeks' duration, the total duration of the second case was about nine days.

Neither clinically nor histologically is there any doubt as to the occurrence of interstitial myocarditis (with or without degeneration of muscle

influenzal pneumonia during an epidemic (Wollenman and Finland; Mulder and Stuart; Jennings). Staphylococcal infection has an unfavorable influence on the resistance of the epithelium to infection with influenza. On the other hand, the penetration of staphylococci is apparently facilitated by the epithelial lesions and the pulmonary edema produced by influenza virus (Verlinde and Makstenieks).

According to Mulder and Stuart influenza bronchitis and bronchiolitis is seen at all ages and is a serious condition in elderly persons and in those afflicted by some chronic disease of the respiratory tract or the heart. It varies in severity but usually clears up promptly in patients with previously healthy lungs once the temperature is normal. Patients suffering from bronchiolitis usually recover but if the patient has a pre-existing disease, death may occur.

Mulder and Stuart emphasized that consolidation of the lungs may develop during the course of the febrile phase of an influenza infection or may follow after an interval of time which may be brief or may last for some days, during which time the patient may have made an apparent recovery from the primary attack of influenza. There is no constant and invariable clinical picture to which the term "influenzal pneumonia" can be applied. But fulminant cases present a characteristic picture and, if for no other reasons, the term "influenzal pneumonia" deserves to be retained to draw attention to these patients. In the most fulminant cases dyspnea, bloody sputum, cyanosis and circulatory collapse may be the main findings and death may supervene within 24 to 48 hours. Physical signs of consolidation are frequently observed, râles, weak breath sounds or patchy bronchial breathing are the chief findings at first, later the classical picture of pneumonia and its complications may develop. The occurrence of a feeble, rapid pulse, low blood pressure, cyanosis, cold extremities and sweating may indicate peripheral circulatory collapse which occurs in the severest clinical grades of pneumonia Then, the patient with influenzal-staphyloccal pneumonia may resemble superficially a case of myocardial infarction with resultant pulmonary edema and a shock-like state.

Parker, Joliffe, Barnes and Finland described two cases of influenza. One individual died of heart failure and the other of pneumonia. Necrotizing lesions of bronchi and bronchioli did not occur in their uncomplicated cases of influenza pneumonia. In the fatal case of heart failure the cellular reaction in the lungs consisted of perivascular round cell infiltra-

Mild myocarditis during and after influenza occurs more frequently than the rare fatal cases, it often appears in a subclinical form and not rarely remains unrecognized. The main symptoms of *mild myocarditis* after influenza are lassitude and often pain in the cardial region.

Frequently there is a subfebrile temperature, sometimes a rapid pulse out of proportion to the temperature, frequently a slow pulse, hypotension, further accelerated sedimentation of erythrocytes. An electrocardiogram should be taken in suspect cases, and the period of observation should be prolonged until normal tracings are obtained, or until progressing of abnormalities stops. The occurrence of electrocardiographic changes and their slow disappearance during and after the infection speaks for the presence of myocardial foci in connection with influenza. These changes are at a maximum in the first week after fever has subsided. They disappear within two or three weeks, although in rare cases it may take months In mild cases the electrocardiographic findings were various: arrhythmias, inversion of T waves in lead I and lead II and in chest leads and prolongation of the PR interval But changes in the electrocardiogram *during and after influenza may* be produced by a combination of forces which are very different, such forces are infection, autonomous imbalance, drugs, aging, concentration of certain electrolytes, the position of the patient It is often impossible to make a decision as to the causation of the electrocardiographic alteration in a particular case of influenza.

The mildness of symptoms in influenza may be due to the diffuse distribution of some inflammatory lesion in the heart so that they produce insignificant or scarcely any electrocardiographic or other disturbances at all Getting up from bed too early after an attack of influenza, or insufficient bedrest during the attack, serves—although *involuntarily*—as an "effort test" Myocarditis was suspected when, after the patient had already got up or when there had not been any sufficient bedrest at all, subfebrile temperature, fatigue and pain in the cardiac region occurred. The symptoms were relieved by renewed and complete confinement to bed The appearance and disappearance of myocarditis could be followed by serial electrocardiograms Recovery could be assumed when the effort test of getting up was *not followed by signs or* symptoms of myocarditis, and a consequent early institution of complete bed rest will effect recovery.

Prolongation of the duration of the QT interval may occasionally occur in influenza (Lyon) The finding of a prolonged QT interval represents a manifestation of the impairment of the functional integrity of the myocardium In such patients there is often a tendency to fainting. These

fibres) in connection with influenza although an exact etiologic-bacteriological cause may be clarified only in exceptional cases. According to Finland, et al. a review of the literature of the pathologic changes in the myocardium in influenza reveals considerable differences in opinion. Leichtenstern described the picture of severe and occasionally fatal myocarditis after an uncomplicated influenza. He observed that death usually occurred during convalescence and that danger to the heart was greatest if there had been morbid changes previously. This author stated that the changes in the heart were due to complicating infections of the lungs and that such alterations were found in any acute infection (parenchymatous and fatty degeneration).

Kuczinski and Wolff observed that the myocardium showed no characteristic morphologic changes in their influenza cases. Opie stated that the heart muscle showed little evidence of injury, as did Klotz, Winternitz, Wegelin.

Lucke, Wright and Kime described cloudy swelling and edema of interstitial tissue of the heart Kirch reported degenerative changes in the myocardium but only very exceptionally inflammatory alterations in the late stages of the disease. Schmorl stated that he had never seen such widespread and extensive myocardial damage in any other infectious disease. According to Roulet the role of mixed infections is probably much more important in causing damage to the heart than the causal agent of influenza

In Wuhrmann's opinion influenza had already subsided when severe cardiac involvement set in as though it came as a "second disease." Whether this presupposed a renewed infection or whether the original infection had spread he could not decide. In any event, those patients whose hearts had not been normal previously were in particular danger. In the severe cases of mainly interstitial myocarditis, heart failure occupied the foreground Electrocardiographic findings in his cases were usually slight or negative There was an increased sedimentation rate of erythrocytes, increased globulins, leucocytosis and shift to the left of leucocytes as well as subfebrile temperatures. According to Finland et al. the cardiac disturbances in influenza were bradycardia, extrasystoles, partial and complete heart block, sinus nodal block, alterations of the various complexes and T wave changes in the electrocardiogram Hypotension has been frequently observed. The symptoms described as accompanying included weakness, dyspnea, palpitations, anginal pain, extreme malaise and Adams-Stokes attacks, and even sudden death may occur.

observed. Also at this stage there is not clear-cut sympathicotonia. We find a lability of function of the autonomous nervous system; the blood pressure and the pulse rate already vary widely during the first few days of the disease. In the second stage, when fever subsides, vagotonic-trophotrope symptoms are obvious, the blood pressure decreases, bradycardia is often present although in a number of cases sympathotonic symptoms remain predominant. Earlier instability is no prerequisite condition for these prolonged and increased reactions to influenza. In Leu's opinion, the influenzal infection is likely to disturb the equilibrium of the autonomous nervous system *for some time* in a measure, as it occurs in patients with autonomous instability "naturally," i e. through their constitution. But among individuals in whom (owing to constitution and heredity) there is anyway an increased tendency of the vegetative centers to react differently, influenza seems to be particularly prone to elicit rapid and intense reactions on the part of the circulation, particularly beyond the fortieth year of life. *Acute neurocirculatory asthenia is the most frequent* cardiovascular complication of influenza Its symptoms are fatigue, weakness, chest or precordial pain and tenderness, palpitations, dizziness, fainting, and dyspnea There is tachycardia, while the size of the heart and cardiac sounds are normal The blood pressure is sometimes elevated but labile. In mild cases there is only an abnormal pulse rate and palpitations, while in more severe cases angina pectoris-like symptoms have been observed Electrocardiographic alterations are usually absent but in several cases some of the T waves were flat, even inverted. These alterations may be very labile

The significance of neurocirculatory asthenia is usually underrated, and the resulting disturbances of the circulatory dynamics require close attention. According to Schimert, the dysfunction of the autonomous centers represents, perhaps, the most important reason for the breakdown of the circulatory economy. In sympathicotonic overactivity—as distinguished from vagotonic overactivity—the heart is exposed to the danger of coronary insufficiency in spite of an increased coronary blood flow. In *vagotonia* the oxygen economizing effect is more important for the heart than the influence of increased vasoconstriction of the coronary arteries The strain on the coronary blood vessels in patients with predominant sympathetic imbalance is increased in accordance with the high oxygen requirement of the heart which runs parallel with the increase of mechanical activity (Schimert and Zickgraf). Therefore, in

cases should be distinguished from fainting of a different etiology in the early convalescence of influenza such as neurocirculatory asthenia or vasomotor imbalance. In the presence of an energetic cardiac insufficiency the QT interval is prolonged. According to Hegglin the picture of an energetic (sometimes plus dynamic) cardiac insufficiency of the heart may be similar to that occurring after myocardial infarction. In both the pulse is small, the blood pressure low. Differential-diagnostically energetic cardiac insufficiency should be distinguished from peripheral collapse which is not accompanied by electrocardiographic changes, and in which the shortening of the Q-second heart sound is also absent. However, the measurements of the QT interval may only be useful if there is no hypertension, cardiovascular disease or arteriosclerotic heart disease, since these types of heart diseases also show a prolongation of the QT interval (Hegglin, Alexander, Ferrer, Harvey and Cornaud).

In two of Lyon's cases there was a reversible energetic insufficiency of the heart following influenza. In these cases the electro-cardiographic findings were chiefly instrumental in establishing the correct diagnosis in cases where episodes of dizziness, fainting and exhaustion were present. The measured QT was greater than the upper limit of normal. One of the cases was complicated by tonsillitis, the other by hyperthyroidism. The disappearance of the prolongation of the QT after recovery from complicated influenza showed the significance of the infection for the causation of that disturbance.

Acute neurocirculatory asthenia is a common accompaniment of infection though the reverse is not true (White). Thus neurocirculatory asthenia is a frequent complication of influenza (Bramwell and King). In these cases it results from the infection and/or from acute strain. According to White we must (until we know more about it) regard circulatory asthenia as a disorder of the autonomic nervous system. In Burnet's opinion, the typical toxic onset of influenza is in all probability accounted for by the absorption of products of the widespread almost simultaneous damage to the epithelial cells It has been assumed that in influenza the autonomous imbalance may be produced by products of degradation and by absorption of concomitant bacteria and their toxins. This central vegetative disturbance manifests itself by a state of irritation of the entire circulation. In the first days of influenza, when fever is rising, sympathotonic-ergotrope signs and symptoms such as rise in blood pressure, tachycardia, palpitations, sometimes precordial pain, are frequently

body. The question arises as to whether the influenzal infection and its complications should be treated with antibiotics (penicillin, streptomycin, Aureomycin, Chloromycetin, Terramycin). Mulder and Stuart-Harris stressed the *need* for early antibiotic and sulfonamide therapy of influenzal pneumonia adjusted for conditions arising from different causative organisms The declining of mortality among the lower age group may be a result of chemotherapeutic agents now available.

Horsfall thought that antibiotics do not produce favorable results and do not shorten the period of influenza. Others believe that the degree of improvement produced by the use of antibiotics is considerable. The effect may be on secondary bacterial infection. Antibiotics are indicated in all influenza patients who are gravely ill, pneumonia and *myocarditis may* be improved or even avoided by this treatment

In influenzal pneumonia with subsequent hemodynamic deficiency, infusions of whole blood, plasma and plasma expanders (Periston, Periston N, Plasmosan, dextran, plus norepinephrine) are indicated. In acute cor pulmonale intravenous infusions should be discontinued. Overloading the circulation with fluids *especially by the intravenous route may* produce pulmonary edema Rapid digitalization is essential. Oxygen therapy for cyanotic and dyspneic cases is sometimes helpful.

As myocarditis is diagnosed, even when there is only a suspicion that it may be present, the patient should be strictly confined to bed. It is of greatest importance to reduce the amount of work imposed on the heart. Sedatives often ensure the desired relaxation Nikethamide, leptazol, caffeine, norepinephrine are used to prevent a too pronounced hypotonia.

The treatment of energetic (plus dynamic) insufficiency of the heart in influenza has been confined to strict bed rest and Bedilanid intravenously.

In severe cases of acute neurocirculatory asthenia drugs with a peripheral circulatory effect *may* be required during the early stages. In most cases of neurocirculatory insufficiency the exhaustion of the patient is the result of the excessive energy expenditure by the body owing to the overactivity of the autonomous nervous system The patient's activity should be restricted Fatigue, weakness, exhaustion require sedation rather than stimulation by tonics The patient should not be aroused to action; he needs rest for maintenance and for restoration Apart from strict bed rest, this is safely and effectively achieved by Bellergal (Bellafolin plus Gynergen plus Phenobarbitone) The total effect is an integrated sedation of the entire autonomous nervous system. The usual dose is four tablets

severe cases of acute neurocirculatory asthenia with sympathetic predominance the coronary blood flow is relatively reduced. Raab draws attention to the cardiotoxic effect of the sudden release of certain amounts of sympathicomimetic amines. A fatal outcome of acute neurocirculatory asthenia as a consequence of exaggerated cardiovascular mobilization alone is not known. It is not, however, altogether impossible that where the heart is directly damaged by influenza and where there has been cardiac damage prior to the influenzal infection, the vegetative circulatory disorder occurring in conjunction with the infection may for once have a worse prognosis. Severe cases of acute neurocirculatory asthenia with coronary insufficiency following influenza are by no means rare. In acute cases after influenza the sympathetically produced exaggerated cardiovascular mobilization has to be reduced. The prognosis of uncomplicated cases is not bad. Recovery from a considerable degree of acute neurocirculatory asthenia is usual. But very often, in severe cases the period of incapacitation lasts for more than one or two months In the influenzal infection neurocirculatory disorder is often of greater significance than a coexisting myocarditis because it may persist much longer than the often very transitory appearance of inflammatory cardiac lesions.

Summarizing it can be stated that the influenzal infection may cause the following cardiovascular disturbances of which we know:

1) Pulmonary capillary damage and subsequent peripheral circulatory disturbances in the case of influenzal pneumonia.

2) Myocarditis—irreversible in fatal cases, reversible in mild and moderate cases.

3) QT prolongation of the electrocardiogram as a sign of impairment of the myocardium, cases are mostly reversible, but rare.

4) Acute neurocirculatory asthenia, a disorder of the autonomous nervous system; cases are frequent and curable

The cardiovascular disturbances may occur alone or in combination with one another.

* * *

In many complications of influenza the causative virus is not the only responsible agent. The influenza virus, by damaging the mucosa of the respiratory tract and the pulmonary capillary bed, breaks down the defense against the bacteria and helps to open the way for the development of superimposed bacterial infection on this occasion The influenza virus together with other pathogens may be deposited elsewhere in the

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2. Virus Pneumonia

The term "virus pneumonia" refers to an acute pulmonary infection, that does not conform to the usual pattern of bacterial pneumonia either clinically, radiologically or therapeutically. It is difficult to find cases of pneumonia where it can be said with certainty that the virus alone is operative (Jennings). Virus pneumonia resembles several viral and rickettsial infections in which laboratory data determine the etiological agent. In those cases the term virus pneumonia should be replaced by the specific etiological one such as ornithosis, psittacosis, influenza A or B, Q fever, etc Clinically it may be difficult, even impossible to establish the etiology in a case of virus pneumonia, but a virus diagnostic laboratory can differentiate serologically between influenza, psittacosis, lymphocytic choriomeningitis, Q fever and the atypical pneumonia of viral origin associated with cold agglutinins and antibodies against non-hemolytic streptococci known as the "M. G" or other strains. If this differentiation is impossible, a *heterogenous group of diseases is treated as a single disease.* The general term virus pneumonia means, for all practical intents, that many other virus infections are included as well as the infection caused by the *yet undiscovered virus of* "primary atypical pneumonia" The term "primary atypical pneumonia" is ambiguous; any pneumonia regardless of cause whose characteristics differ from classic pneumonia *is atypical. The terminology, whether* virus pneumonia or atypical pneumonia is used, remains unsatisfactory.

Virus pneumonia is an acute infectious disease characterized by fever, severe headache, cough and other respiratory symptoms, and by radiographically demonstrable densities (Reimann; Smiley, Showacre, Lee and Ferris) In severe cases increasing dyspnea, cyanosis, delirium, coma and death may occur. The frequency of virus pneumonia in general practice is

daily, in severe cases the dosage may be increased up to six daily. After two or three weeks the dosage can be gradually reduced. Many patients show a remarkable tolerance to this combination of drugs and are relieved by this treatment from exhaustion, oppression, and palpitations. Improvement not only concerns subjective complaints but also an objective reduction of exaggerated cardiovascular mobilization although, as a matter of fact, complete recovery can sometimes only be effected after several months.

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of the respiratory tract. Some virus pneumonias give positive Wassermann, Kahn and citochol tests, but negative Meinecke reactions. The occurrence of hemolytic anemia in virus pneumonia has been frequently reported.

Characteristic histologic changes noted in the lungs of eight cases of viral pneumonia have been reported by Parker, Joliffe and Finland. There was a mononuclear type of alveolar exudate, and interstitial infiltration predominantly of plasma cells, swelling and proliferation of alveolar lining cells A hyaline-like membrane within the alveoli was found in half the cases. While the bronchioles not infrequently contained polymorphonuclear leucocytes and, occasionally, some bacteria, their walls were infiltrated by mononuclear cells, and the epithelium was intact. Bacterial infection played a minor role except in two cases in which there was some abscess formation. There was occasionally a focal infiltration of few large mononuclear plasma- and mast-cells in the interstitial tissue of the myocardium or subendocardial hemorrhages extending into the adjacent myocardium and necrosis of myocardial fibres Sometimes a hemorrhagic fluid was found in the pericardial sac Gore and Saphir found myocarditis in 32 of 322 patients with virus pneumonia.

Cardiovascular involvement is not regarded as a conspicuous feature in mild and moderate cases of virus pneumonia but it occurs in adults and children In severe cases respiratory embarrassment, cyanosis, drop in blood pressure, relative bradycardia or tachycardia, peripheral circulatory collapse may occur with fatal outcome Electrocardiographic alterations have been observed in severe cases of viral pneumonia with fatal outcome. Sinoauricular tachycardia, low T_1 and T_2, inverted T_3 and notched T_4 waves were interpreted as myocardial damage or digitalis effect in a fatal case by Parker, Joliffe and Finland

According to Painton, Hicks and Hantman, virus pneumonia may also be associated with myocarditis in not too severe cases They found electrocardiographic abnormalities which had a temporary existence for a period of several weeks or some months before returning to normal Only a few electrocardiographic alterations persisted longer

In a series of virus pneumonias observed during the years 1950 to 1952 in Jerusalem, several cases showed transient electrocardiographic changes (flat or inverted T waves, abnormal ST segments, abnormal P waves). The physical cardiac findings were normal, the heart was normal in size and shape Auscultation revealed pure heart sounds, the pulse was accelerated or slow There was a transient drop in blood pressure for various periods

unknown and varies widely in different areas and at different times of the year. The disease attacks all age groups and occurs both endemically and epidemically.

Virus pneumonia is often a mild, even ambulatory disease but is occasionally a severe illness presenting an extensive type of pneumonia. Viral causation was formerly suspected in cases where there was no response to sulfonamides and penicillin. After an incubation period of 7 to 21 days, the following clinical features are established: The onset is gradual. Initial complaints are fatigue, malaise, weakness, chilliness and headache. There is nasal congestion, hoarseness, pharyngitis, dry cough, chest pain, sometimes abdominal pain and vomiting. Fever is occasionally present for no longer than the first 48 hours, but may also last from some days to several weeks. Physical signs in the chest are scarce or absent. Areas of dullness posteriorly, some moist râles, harsh breath sounds, loud rhonchi or suppression of breath sounds may be present. In the extensive type increasing numbers of crepitant râles are heard throughout the lungs, but there are occasionally persistent areas of consolidation, clinically demonstrable The pulse is often slow, and the blood pressure normal or low The sputum, if present, is scanty, mucoid or mucopurulent, sometimes blood-streaked and does not contain pathogens which are usually associated with bacterial pneumonia

The radiological appearance varies in the individual cases of virus pneumonia. There may be unilateral, fan shaped infiltration of one of the lower lobes or dense hilar or perhilar shadows with radiating, mottled densities. In severe cases an extensive miliary, soft, nodular type of density in both lungs may be present Sometimes virus pneumonia migrates from one lobe to another. Positive roentgen findings may last for up to eight weeks.

The blood cell count may be normal or show leucocytosis In severe cases the serum proteins are reduced and there may be a temporary rise of nonprotein nitrogen in the blood There are two nonspecific tests that help to define, at least one group of virus pneumonia They consist in the demonstration of cold hemagglutinins to a titer of from 1:40 and upwards and agglutinins for indifferent streptococci such as "M G." or "344" strains. The streptococcal agglutinin is unrelated to the cold hemagglutinin. A fourfold or greater increase is only rarely found except in viral pneumonia. But unfortunately neither test gives positive results in all cases and cold agglutinins are not specific to one specific virus infection

According to Colmers and Snavely, cold sponges, administration of antipyretic drugs and *ordinary exposure*—*routine* procedures in the treatment of febrile patients—may be factors in the production of acute hemolytic anemia in patients with high cold hemagglutinins. According to Carey, Wilson and Tamerin, it may be pertinent to recommend that in the treatment of acute embolism or thrombosis of a limb when the application of ice is contemplated, the presence of hemagglutinins has to be previously ruled out. The recognition of the cause of cyanosis of fingers, toes, nose and ears on exposure which are produced by the development of cold hemagglutinins in virus pneumonia should make severe sequelae avoidable by rigid precaution against chilling and unnecessary exposure.

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3 Interstitial Pneumonia in Infants

Infants may develop pulmonary infections from various causes; but it is highly probable that many pneumonias are due to viruses. The virus of measles produces a variable degree of respiratory involvement and high incidence of pulmonary infiltration even in mild cases. Poliomyelitis may cause instances of interstitial pneumonia. Saphir observed six instances of interstitial pneumonia in 17 cases of poliomyelitis. Jurow and Dolgopol found it in 31 cases of 121 fatal cases, i.e. in 25 6 per cent of all his poliomyelitis cases. It occurred either as the only pneumonic process or in combination with some other forms of pneumonia. Ephrati-Elizur, Bernkopf

of time. In these cases apart from bed rest no special treatment was necessary.

Pericarditis has been noted to follow an atypical pneumonia by Fuller and Quinlax; Finkelstein and Klainer; Higley, Warren and Harrison. Mild, moderate or severe substernal pain after viral pneumonia may be due to a pericarditis with and without effusion. In patients with atypical pneumonia, pericarditis may be recognized with the aid of serial electrocardiograms (Bower, Gerrard and MacGregor; Levy and Patterson).

Reich, Ciaiolo and Reinhart administered, in 10 cases of virus pneumonia with massive bilateral pulmonary involvement, 15 transfusions of 250 to 500 cc. of convalescent whole blood and sulfonamide and penicillin. Although the patients were severely dyspneic and threatened with circulatory collapse, they all recovered. Greater amounts of blood were not used to avoid overloading the heart. But in very severe cases, observed by Parker, Joliffe and Finland, oxygen under positive pressure and daily plasma infusions of 250 to 500 cc. to a total of 2500 cc. gave only partial, if any, relief in the later stages of the illness. Patients with any evidence of myocarditis or cardiovascular failure should have prolonged bed rest and gradual resumption of activity.

The presence of cold agglutinins in titer above 1:40, unusual except in virus pneumonia, has important diagnostic significance. The action of cold agglutinins on the red cells of the patients may clinically produce cyanosis of the parts of the body which are exposed to environmental temperature. Cyanosis affects the ears, nose, fingers and toes especially in patients where maximum titers are present The titer of cold agglutinins is generally proportional to the severity and duration of the virus pneumonia and may, in some patients, remain elevated for 2 to 10 months. Peripheral vascular occlusion, pulmonary infarction, phlebothrombosis, hemolytic anemia may develop in patients with viral pneumonia whose serum contains hemagglutinins in high titers and in high thermal amplitudes. In these cases intravascular hemolysis occurs.

McNeil offered a possible explanation for the coincidence of high agglutinin titer and marked pulmonary edema with hemorrhagic infarction. It seems logical to him that small groups of agglutinated cells might form in a relatively cold extremity, act as multiple emboli and cause the pulmonary infection picture. Death may be so rapid that organization of these emboli would not take place Large masses of these and blood cells may remain compact upon reaching the lung.

of the five cases died suddenly, two of them without any apparent previous signs of illness. One case showed acute dilatation of the right cardiac ventricle. Epithelial giant cells were found in the alveoli and bronchi. They contained cytoplasmic inclusion bodies. Besides the findings of interstitial pneumonia, there was pathological evidence of generalized lymphatic tissue involvement.

Interstitial giant cell pneumonia was considered *to be due to virus*. The relationship of giant cell pneumonia to canine distemper has not as yet a clinical or epidemiological basis In none of their cases was there any evidence of direct contact with dogs.

This illness is not such a rarity as the paucity of pathological reports seems to indicate The apparent rarity might be due to the frequent presence of secondary invaders which masks the original picture, and to the possibility that the autopsy is rarely performed at the giant cell stage of the disease.

It is suggested that interstitial giant cell pneumonia and virus pneumonia of infants represent a single disease entity caused by virus.

In a second paper, Wolman, Izak and Mundel report on interstitial pneumonia which occurs in Israel in a great number of infants below the age of two years The authors *maintain that interstitial pneumonia* was in a certain year a major cause of death among infants, accounting for over 15 per cent of all deaths in the age group of 0–2 years (and especially frequent among prematures) in Jerusalem The infection occurs sporadically and epidemically

Interstitial pneumonia may have a chemical, metabolic, vascular, protozoal, rickettsial or viral etiology, but it seems possible *that most interstitial pneumonias* in these infants are due to viruses The authors stated that thickening of the alveolar septa of the lung produced by the presence of mononuclear cells was a satisfactory criterion for the histologic diagnosis. In some cases they have found cytoplasmic inclusion bodies in cells of the pulmonary *interstitial infiltrates, in* epithelial cells of the respiratory and gastrointestinal tract The pathological lesion is mostly patchy. The presence of giant cells, the nature of the *interstitial exudate*, the occurrence of interstitial hemorrhages do not constitute, in the authors' opinion, sufficient reason for subdividing the process Pathological findings included in *addition to the interstitial* pneumonia, frequent superimposed bronchitis and bronchopneumonia, subserous and parenchymatous hemorrhages, diffuse involvement of lymphatic tissues, necrosis and

and Wolman reported interstitial pneumonia produced by ornithosis virus in two children.

Adams described a clinical entity of primary pneumonia. The infection affects young full-term and premature infants, also older infants and children. The condition may occur sporadically and epidemically. The incubation period is about seven days. Symptoms of the disease vary from sneezing and mild cough to severe cough, dyspnea and cyanosis. The disease has a diphasic temperature curve. The case fatality rate is high; nearly 30 per cent died of hemorrhagic pneumonia. The lungs showed proliferation, destruction of the pulmonary epithelium and a predominant mononuclear exudate. The etiology was uncertain. Cytoplasmic inclusion bodies were found in the epithelial structure of the lungs and bronchi. Adams found also eosinophilic inclusion bodies in the cytoplasm of epithelial cells in pharyngeal smears, he considered such findings as helpful in diagnosis. Ingleby found inclusion bodies in various organs and Goodpasture, Averbach, Swanson and Cotter described nuclear inclusion bodies in the tracheal and bronchial epithelium of such children.

The occurrence of fatal interstitial pneumonia in prematures by viral infection has also been observed by Freudenberg and Tobler, Gormsen, Weisse, Boemke and Piroth Freudenberg and Tobler assumed a viral infection because bacteria could never be found Weller, who described the fatal course of the disease in one patient, reported the findings of multinucleated giant cells in alveoli, alveolar walls and bronchioli In these cells nuclear inclusions were prominent. The lesions were similar to those seen in canine distemper, a disease of which man has been said to be an asymptomatic carrier Adams reported experimental evidence of a relation between respiratory disease of man and canine distemper. Using ferrets and chick embryos, human serum and human gamma globulin were compared with hyperimmune distemper antiserum and ferret immune serum. Controls were used in each experiment. Neutralization of distemper viral infection in ferrets was accomplished, and infection caused by the virus in living chick embryo was neutralized by human sera and human gamma globulin. Inclusion bodies with the same morphologic and staining qualities were demonstrated in infected human and animal tissues. Adams believed that these results indicated a possible direct relationship between distemper in dogs and human primary pneumonitis.

Wolman, Izak, Freund and Shamir described clinical and pathological changes in five infants dying from interstitial giant cell pneumonia. Three

Periston or Periston N may occasionally be capable of reducing the danger of peripheral circulatory collapse. According to Kosenow, absolute rest in bed, cardiac and circulatory drugs and oxygen inhalation are necessary in the management of interstitial pneumonia of infancy.

Recently some authors found a protozoon, termed *Pneumocystis carinii*, as presumable cause of interstitial pneumonia; other authors are of the opinion that yeasts rather than protozoa are dealt with and suggested the term pulmonary blastomycosis or yeast pneumonia for the disease under consideration. Whether these theories refute the virus etiology cannot as yet be decided, but further corroboration is required. In the opinion of Kosenow yeasts are frequently found in pharyngeal smears of healthy infants and infants with diseases other than interstitial pneumonia.

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4. Psittacosis, Ornithosis, Lymphopathia Venereum, Cat Scratch Disease

The work of the last decade has brought a large increase of viruses belonging to the psittacosis-lymphopathia venereum group. In 1939, from members of this family responsible for human diseases there were psittacosis, lymphopathia venereum, trachoma and inclusion conjunctivitis.

interstitial infiltrations in various organs and frequent association with congenital malformations. Interstitial myocarditis has been observed in some cases.

The most important clinical findings were: dyspnea, cyanosis associated with few physical findings in the chest, gastro-intestinal symptoms; and sudden as well as unexpected death was frequent. According to Kosenow, there are three cardinal symptoms in this disease: accelerated respiration, violent attacks of cough and pale cyanosis.

The general picture of the viral interstitial pneumonia of infants is that of a patchy pneumonia. With the exception of inclusion bodies, none of the pulmonary changes are peculiar to the pneumonia or pneumonitis of infancy. They have all been found in other types of virus pneumonia, i e. in ornithosis, influenza, varicella, poliomyelitis, and measles.

It seems that an important factor in the fatal outcome of interstitial pneumonia of infancy is the widespread pulmonary vascular damage which may lead to peripheral circulatory collapse. Other factors such as myocarditis, malnutrition also play a certain role. The danger of peripheral circulatory collapse associated with interstitial pneumonia is immense and is produced by the increased permeability of pulmonary capillaries, and consequent escape of protein and electrolytes into the tissues.

Freudenberg and Tobler tried Aureomycin and Chloromycetin in 15 cases of interstitial pneumonia of premature babies but this treatment proved to be of doubtful value. Other authors believe that Chloromycetin appears to be curative (Schmöger).

In the cases of Wolman, Izak and Mundel, the infants received antibiotics. It was impossible to tell whether their treatment was of value. A morphologic difference of cases with and without treatment with antibiotics was not demonstrable.

Antibiotics are indicated in the treatment of interstitial pneumonia in view of the fact that there is frequently a superimposed bacterial bronchitis and bronchopneumonia.

Adams, Green, Evans and Beach emphasized that infants with primary virus pneumonitis do not tolerate much parenteral fluids. But transfusions of whole blood or administration of plasma should be employed as indicated for anemia or protein deficiency Oxygen therapy should be given at the earliest appearance of dyspnea and cyanosis, using either a mask or tent so that the oxygen concentration can be maintained between 40 and 60 per cent.

Lymphopathia venereum and cat scratch disease are more than infections localized in some lymph nodes, for other changes may occur in both. But, on the other hand, in cases of human psittacosis the lungs are not always involved and recognizable clinical signs and symptoms of illness may be absent in human carriers of psittacosis virus.

Psittacosis is usually a disease characterized by fever, pulmonary, circulatory and central nervous system involvement, and prostration. It is conveyed by a bird of the psittacine family or by man. The virus is present in the feces and nasopharyngeal droplets of the bird. Infection in man follows inhalation of the droplets or infected dust that arises from feathers of the birds. The virus has been easily isolated from the blood of human psittacosis cases, from throat washings and from sputum, when mouse inoculation was introduced Complement fixation antibodies appear in the serum after the onset of symptoms and rise during the progress of the infection.

Ornithosis is a name given to similar infections in birds other than parrots (doves, pigeons, chickens, ducks, pheasants, canaries, turkeys, fulmars). Pigeons are known to be extensively infected with ornithosis virus in America, England, Australia, Germany, France, Belgium and Israel. Severe human cases have been contracted from pigeons. Psittacosis is associated more with noticeable symptoms of a severe disease, but ornithosis has frequently a lower virulence and is rarely fatal. According to Tobin the virus of ornithosis produces in men "atypical pneumonia" but the severity of the infection varies considerably from inapparent to severe infection ending in death.

The incubation of psittacosis is six to fourteen days. The onset is sudden. The patient presents shivering, headache, nausea, vomiting or diarrhoea, sore throat and nose bleed Temperature may be high and continuous and falls by lysis In the course of the first week bronchitis or bronchopneumonia usually appear In the second week cardiovascular involvement is frequent, but may be altogether absent In the early course of illness there is no dyspnea and cyanosis, the pulse is slow, only in severe cases rapid and weak In the second week cyanosis, dyspnea, and sometimes collapse, may develop Central nervous system involvement or abdominal symptoms are additional features The disease may last three to four weeks and convalescence is often slow The mortality of adults was twenty to forty per cent in the preantibiotic age The prognosis was worse in older persons, but today it is much better when early antibiotic therapy is used.

Today we have many strains of psittacosis virus derived from non-psittacine birds and differing sufficiently from the original parrot strain, to deserve the characteristic name of ornithosis. There is an ever increasing number of new mammalian viruses of this group.

Non-avian strains of psittacosis virus which have been isolated from outbreaks of virus pneumonia in man, are the San Francisco, the Louisiana and the Illinois pneumonitis viruses. The virulence of these strains and the promptness with which they pass from person to person had lead to the suggestion that they may be man-adapted strains of psittacosis virus and use him as their principal host The viruses of the psittacosis-lymphopathia venereum group have important characteristics in common i.e. relatively large size, certain staining properties, the development cycle. They have—with the possible exception of the viruses of trachoma and inclusion conjunctivitis—a common antigen, a heat-stable important constituent which tends to dominate serological reactions with these viruses (Bedson). These viruses are distinct entities On the basis of complement fixation tests, they are antigenetically closely related but virus-neutralization tests conducted in mice show antigenic differences.

Lymphopathia venereum displays chiefly a genito-rectal, and occasionally, an oculo-glandular syndrome. Trachoma and inclusion conjunctivitis usually produce only mucosal disturbances. Abu-Jaudeh recently emphasized contrary to the accepted concept, that trachoma is not a local disease of the conjunctiva but rather a widespread affection involving most of the epithelial surfaces of the body On the basis of clinical and microscopic evidence trachomatous rhinitis and, possibly, urethritis should be recognized as clinical entities.

A new clinical entity—belonging to the psittacosis, lymphopathia venereum group—is cat-scratch disease (benign inoculation lymphoreticulosis, acute benign regional lymphadenitis) occasionally an oculo-glandular syndrome or even associated with encephalitis Histological changes have been observed in lymph nodes which resemble those found in lymphopathia venereum. Mollaret, Reilly, Bastin and Tournier announced the discovery of the particular virus causing the disease This, together with the demonstration that the serum from a number of cases of cat-scratch-fever, gives a positive complement fixation with a psittacosis-lymphopathia venereum group antigen, implies that the agent of cat-scratch-fever may be classified to this group. The disease is thought to be caused by a virus for which the cats may act merely as passive carriers.

alveoli and a proliferation and desquamation of these cells. Considerable variability is exhibited in the character of the cellular content in different alveoli. Many other organs are more or less affected by this infection. Elementary bodies appeared as intracytoplasmic basophil inclusion bodies within alveolar cells, macrophages of splenic sinuses and in Kupffer cells and elsewhere.

The cardiovascular system in human cases of psittacosis often shows alterations. Dilation of the right side of the heart, especially of the right auricle, hypertrophy of cardiac muscle, cloudy swelling and fatty degeneration of the myocardium, interstitial edema, interstitial infiltration (with plasma cells and lymphocytes) subendocardial hemorrhages especially in the region of the mitral, aortic and bicuspid valves have been reported by Adamy, Hutchinson, Rowlands and Simpson; Polayes and Lederer, Wuhrmann, Boemke and Piroth.

Cases of psittacosis running a severe course or ending fatally are characterized by circulatory and/or cardiac failure. Death often occurs between the tenth and twelfth day of illness. Even if recovery takes place, there is danger of myocardial involvement which Adamy has termed "postinfectious myocardial degeneration." The myocardial damage may extend far into the period of convalescence Wuhrmann described a case of psittacosis in a man, 40 years of age, myocarditis was the cause of unexpected death during the convalescence. The patient had already overcome the general infection Flat T waves in an electrocardiogram suggested myocardial involvement. Tachycardia was present several days prior to death. The heart damage was an interstitial myocarditis, especially of the right heart and mainly of the right auricle and some myolysis. When dealing with psittacosis good care should be taken of the heart and circulation.

In ornithosis, too, where cardiovascular involvement is generally less pronounced, heart and circulation are more or less severely affected in some cases. Interstitial myocarditis has also been observed in fatal ornithosis of children. Strobel considers hemorrhage from the nose and petechiae as a sign of general vascular damage in ornithosis. The same author mentioned sinustachycardia in one case and persistent tachycardia and flattening of T waves in three limb leads of the electrocardiogram in another case of ornithosis.

Valero reported a case of ornithosis with cardiovascular involvement in a man, 37 years old On the seventh day of illness, the patient developed intense precordial pain, severe mental anguish, hypotension (70/40 mm.

In ornithosis the disease starts with a sudden rise of temperature, headache, photophobia, sweating, malaise, anorexia, dry cough. The fever lasts eight to twenty-eight days. Bradycardia is frequent. X-ray findings of the lungs are more marked, than are physical symptoms and signs referable to the respiratory tract. Sometimes some coarse râles are heard throughout the lungs; dyspnea and weakness are sometimes frequent. Often the symptoms are influenza-like. The pyrexia subsides by lysis. With the antibiotics now in use, many cases are improved in several days. The diagnosis depends on history of contact with birds, the results of laboratory procedures (isolation of the virus) and a demonstration of a rise in titer of complement fixating antibodies.

It is now being recognized that fatal cases of interstitial pneumonia in infants and children are caused by an ornithosis strain. Ephrati-Elizur, Bernkopf, and Wolman reported two cases of fatal ornithosis, one in a two-year old girl, and another in a one-month old baby.

The first child developed cough and râles appeared on both lungs; she died a week later. The other infant died suddenly without previous signs of illness. In both cases there were foci of interstitial mononuclear infiltration in both lungs. The general picture is that of a patchy bronchopneumonia with areas of atelectasis and emphysema. Feulgen-positive cytoplasmic inclusion bodies were found in some of the mononuclear cells and in cells inside the dilated alveolar septa From lung suspensions of each case a virus was isolated which belonged to the psittacosis-lymphopathia venereum group of viruses. The healthy parents of both children reacted positively with the group-specific antigen of the psittacosis-lymphopathia venereum group Complement fixation tests of 27 sera of children suffering from atypical pneumonia were examined serologically and gave positive results with this group specific antigen in seven cases. Mice showed after intranasal and intraperitoneal inoculation characteristic pulmonary changes and died after intracerebral inoculations. Macchiavello stained smears from material of infected mice and of eggs showed typical inclusion and elementary bodies Cross immunization tests carried out with the virus isolated from the first case and a strain of ornithosis virus isolated from pigeons in Israel did not reveal any immunological difference.

The main pathological lesion of psittacosis is a mononuclear infiltration of the interstitial framework of the lungs Frequent is lobar pneumonia with little fibrin in the exudate and swelling of the epithelium lining the

athia may be preceded by a small maculo-papular skin eruption and may be followed by encephalitis According to Usteri, Wegmann and Hedinger the increasing number of observations of cat-scratch disease shows that, apart from cutaneous infections, enteral, bronchogenic and other portals of entry may exist.

There are typical and atypical forms of the disease. Some of the atypical forms can only be explained by assuming a noncutaneous portal of entry. The atypical forms include pseudovenereal forms as well as erythema nodosum-like tonsillar, mesenteric, pulmonary and meningo-encephalitic types. According to Hedinger, there is a cutaneous-glandular, a tonsillar-glandular and an ocular-glandular form, and perhaps an abdominal type of cat-scratch disease It is possible that patients with abdominal pain may have had mesenteric lymphadenitis (Daniels and MacMurray).

An abdominal or mediastinal form of the disease may possibly develop after viral inoculation in the intestinal or respiratory tract (Vivell). The proximity of hilar lymph nodes with extension of the infection into the pericardial sac may be a factor for a possible pericarditis associated with a subacute regional lymphadenitis Although the disease usually follows a benign course, there is some evidence to suggest that the condition may not always be benign or localized in character

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Hg) bradycardia (48) and cyanosis. There was a bronchopneumonia in the right upper lobe. The patient used to feed his pigeons from his own mouth. The close association with pigeons from which Levinthal-Coles-Lillie bodies were isolated and the positive complement fixation for psittacosis in rising titers left no doubt as to the identity of the disease as ornithosis. The case was susceptible to penicillin and the patient recovered completely. Thus, a patient with ornithosis may resemble, superficially, a case of myocardial infarction with a resultant shock-like state. Aureomycin, Chloromycetin, Terramycin in psittacosis and ornithosis influence the course of illness, cutting the number of viral elements to a low level and permit the normal defense mechanism to dispose of the remainder and act on secondary invaders to lessen toxicity and prevent complications. The illness, if treated with antibiotics seems to have a smooth course and it may be possible to avoid severe circulatory complications.

Lymphopathia venereum, (lymphogranuloma venereum, venereal bubo, Durand-Nicolas-Favre disease) is characterized by unilateral or bilateral, often suppurative inguinal lymphadenitis and periadenitis After an incubation period of 3 to 25 days or longer, swelling of lymphatic glands appears in the groin above Poupart's ligament The swelling may increase day by day and is associated with periadenitis. After about a week or longer the affected glands begin to soften and then to suppurate. Lymphadenitis may sometimes appear in the armpit and in the neck There may be iliac lymphadenitis without suppuration Probably lymphopathia venereum develops vascular damage (Coutts and Davila; May, Soriano and Yrastorza). A benign form of pericarditis has been demonstrated in a case of lymphopathia venereum with supraclavicular and mediastinal lymphadenopathia Virus was isolated from a supraclavicular node, there was a high titer of complement fixing antibodies (Sheldon, Wall, Slade and Heyman).

Instances of systemic infection with lymphopathia venereum have been reported but only few of them have been proved by recovery of the virus. But such cases emphasize the systemic nature of lymphopathia venereum, the clinical manifestations of which may not always suggest its venereal origin

Cat-scratch disease is characterized by lymphadenitis which frequently suppurates and heals without a scar The course of the disease is usually mild, but is occasionally accompanied by fever, malaise, anorexia, nausea, weakness, aching, chills, headache or abdominal pain. The lymphadenop-

athia may be preceded by a small maculo-papular skin eruption and may be followed by encephalitis. According to Usteri, Wegmann and Hedinger the increasing number of observations of cat-scratch disease shows that, apart from cutaneous infections, enteral, bronchogenic and other portals of entry may exist.

There are typical and atypical forms of the disease. Some of the atypical forms can only be explained by assuming a noncutaneous portal of entry. The atypical forms include pseudovenereal forms as well as erythema nodosum-like tonsillar, mesenteric, pulmonary and meningo-encephalitic types. According to Hedinger, there is a cutaneous-glandular, a tonsillar-glandular and an ocular-glandular form, and perhaps an abdominal type of cat-scratch disease. It is possible that patients with abdominal pain may have had mesenteric lymphadenitis (Daniels and MacMurray).

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5. Mumps

Mumps (epidemic parotitis) is an acute contagious disease usually characterized by enlargement and tenderness of salivary glands (particularly the parotids), fever, headache, and by a tendency to involve other glands (testes, ovaries, pancreas), the central nervous system, the kidneys and the heart. It is a disease of children and young adults. Although mumps rarely causes death or permanent damage, it is sometimes a serious illness with marked deterioration and a lot of so called complications which really are manifestations of the disease. Mumps is an endemic disease but severe epidemics are also observed (Habel). The virus of mumps has been isolated from secretions of the nose, mouth, blood, cerebrospinal fluid, and testes. Antibodies have been observed in blood and hydrocele fluid. Sera of patients convalescent from mumps fix complement from infected monkey parotid or from virus infected eggs.

The incubation ranges from 18 to 24 days; an invasive period of 12 to 24 hours may occur before involvement of salivary glands is present. Mumps usually disappears within 7 to 10 days. The salivary glands and other glands never suppurate. Mumps has to be considered as systemic disease.

The observations on material of infected parotid glands indicate that the changes consist of an interstitial serofibrinous exudate, leucocytic infiltration, congestion and edema of tissues. The epithelial cells of the excreting ducts show degenerative changes. Edema is present in the interstitial tissues of the pancreas and the testes and in addition destruction of cells throughout the parenchyma and infiltration with round cells. Manca described mumps myocarditis characterized by an interstitial fibrinous inflammation.

Clinically, myocarditis as an accompaniment of mumps has been recorded since 1900. That the heart may become affected in mumps has been known to many physicians. Cases of endocarditis and pericarditis have occasionally been reported. The frequency of bradycardia in mumps patients, especially after the drop of temperature, has been emphasized.

Pujol (1918) found, among 450 cases of mumps, 12 with circulatory disturbances and reported three cases each which manifested clinical evidence of myocardial involvement during convalescence. Barbato (1925) suspected on the basis of clinical observation the presence of mumps myocarditis. Many cases of electrocardiographic alterations are reported in mumps. Wendkos and Noll (1944) reported a case of mumps myocarditis, diagnosed by electrocardiographic examination and described minor T waves alterations, prolongation of the PR interval and bradycardia.

Rosenberg (1945) reported on an epidemic study in which electrocardiographic evidence of cardiac involvement was noted in 16 of 104 cases of mumps or in 15.4 per cent of patients. This indicates that myocardial involvement is no rare event in mumps. Changes in tracings (done serially) may appear between the fifth and tenth day of illness and return to normal within two to thirty-five days or may persist to five months. Only four of sixteen patients had clinical evidence of cardiac involvement. The author believes that the majority of cases of mumps myocarditis follows a subclinical course and requires electrocardiographic studies for recognition. He noted diphasic or inverted P. waves in one or several leads, prolongation of P.R interval, inverted QRS, alterations of the ST segments and inversions of T waves. In several patients there was precordial pain, palpitations, and dyspnea. Felknor and Pullen (1946) contributed an additional case of subacute pericarditis and myocarditis with slight elevation of the S T_1, $_2$, $_3$, low T waves and inverted T_1 and T_4.

Bland (1949) reported a case of mumps associated with myocarditis, meningomyelitis and pancreatitis. Electrocardiographic studies suggested myocardial damage in the lateral wall of the left ventricle. Israel (1953) found in a group of 20 children between the ages of 6 and 10 suffering from mumps, three with prolonged PR interval, one with inverted QRS in lead 2 and CF_4 and one with negative T_1 and T_4, but no other signs and symptoms of cardiac involvement.

Magida reported a case of mumps accompanied by orchitis, pericarditis and serositis with typical electrocardiographic changes occurring during the acute phase of illness extending into the convalescent period. It has been suggested that endocarditis may complicate mumps (Sciaux, 1935).

Cottel and Hauser reported on the case of a 28 year old man in whom mumps was followed, 1 and 2 weeks later respectively, by pulmonary infarction first of the right and then of the left lower lobe although no evidence of thrombophlebitis of the lower extremities was noted. It was assumed that thrombosis of the pelvic veins caused by orchitis was responsible for the pulmonary infarcts.

Elkan reported the case of a 32 year old man in whom mesenterial vascular thrombosis could be traced to an attack of mumps by way of pancreatitis. Wide resection of gangrenous intestinal loops beyond the lesion was performed, and the patient recovered after a stormy postoperative course. Anticoagulant therapy should be started immediately to prevent the spreading of thrombosis.

The whole cardiovascular system deserved attention in cases of mumps.

Bland stresses that mumps goes frequently unrecognized and usually manifests itself in subclinical form. The importance of this recognition lies in the fact that with the knowledge of the possible presence of an associated myocarditis one is more inclined to prolong the period of convalescence.

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6 Cytomegalic Inclusion Disease

Salivary gland virus disease (inclusion disease or cytomegalic inclusion disease) is recognized by characteristic intranuclear and intracytoplasmic cytomegalic inclusion bodies These bodies are found in the salivary glands and the cells of various organs. On microscopic examination it is impossible to overlook the giant cell which contains the intranuclear inclusion bodies Both the cell and the nucleus are extraordinarily large in contrast with the surrounding structures The large inclusion bodies are either acidophilic or basophilic masses, centrally located in the nucleus, with their enlarged nuclei haloed by a clear zone of vacuolated or granulated protoplasm which is peripherally ringed by chromatinic massing along the nuclear membrane, thus presenting an aspect of a bird's or owl's eye (Bacala and Burke, Berton) Cytomegalic inclusions bodies are observed in infants, children and adults In adults they are observed in association with enteritis, pneumonitis, in refractory anemia and necrosis of liver, adrenals and pancreas.

Inclusions bodies have been also observed in the virus disease of guinea pigs known as salivary gland disease and in hamsters, mice, wild rats, moles and monkeys. The human cytomegalic disease is considered viral in nature rather than a product of toxic or degenerative cellular processes.

These viruses are thought to be very species-specific and thus the human strain cannot be transmitted to the experimental animal. Controlled experiments designed to demonstrate diagnostically significant serologic changes in the infected animal have proved inconclusive (Ahvenainen, Betton)

Ribbert first found such parasitized cells in the kidney of a newborn syphilitic infant and in the parotids of two older non-luetic infants. Jesionek and Kiolemenoglou regarded the presence of such protozoan-like cells as a separate entity involving, in their particular case, the kidneys, lungs, and liver of another 8 month syphilitic fetus. Jackson called attention to the similarity of "protozoan parasites" in the organs of infants to cells which have been observed in the salivary glands of guinea pigs. Goodpasture and Talbot recognized the inclusion bodies as such and stressed their resemblance to those found in cutaneous lesions caused by varicella virus They also noted the peculiar changes present in ductal epithelial cells of guinea pig salivary glands, concluding that this cellular transformation was similar to that occurring in the tissues of infants.

Cole and Kuttner described the isolation of virus from the submaxillary glands of guinea pigs

According to Farber and Wolbach, the inclusion bodies found in submaxillary glands of infants are apparently identical with those found in the submaxillary glands of guinea pigs and they are, generally, similar to inclusion bodies which are found in diseases due to filtrable viruses. The histopathology of other intranuclear inclusion body-bearing diseases such as herpes simplex, varicella, etc. appears to us to be very similar to, or even identical with those found in cytomegalic inclusion disease. According to Wyatt, Saxton, Lee and Pinkerton, the etiologic agent of the cytomegalic inclusion disease is a specific virus, which, *per se*, is a common cause of fetal and infantile death The morphology and cytology of the inclusion-bearing cells is pathognomonic of the disease. The virus should be classed as necrotizing rather than saprophytic The increasing incidence of adult involvement since the first case was reported by von Glahn and Pappenheimer is also remarkable Wyatt, Simon, Trumbull and Evans described fulminant salivary gland virus (cytomegalic inclusion) pneumonitis in adults It was suggested, that this type may result from altered susceptibility induced by the action of antimetabolites. For a synopsis of the clinical manifestations, the associated host-parasite relationships, the histopathologic lesions, reference should be made to the papers of Cappell

and McFarlane, Smith and Vellios, Worth and Howard, Kidder, Ahvenainen, Bacala and Burke, Wyatt, Simson, Trumbull and Evans. Myocarditis in salivary virus disease has been reported by Ahvenainen, Bacala and Burke and by Berton (the same case was reported by Worth and Howard).

Ahvenainen recorded five cases of inclusion disease. Two cases were in newborns and three in three month old infants. The case associated with myocarditis was a three month old infant suffering from diarrhoea from the age of one week. Fever lasted some weeks There was pneumonia and meningeal symptoms appeared on the last day of life. Autopsy findings were interstitial pneumonia, mononuclear infiltration of the liver and kidneys, purulent meningitis and encephalitis. Myocarditis was extensive and it was seen in every section. Inclusion bodies were observed in the heart, lungs, liver, spleen, pancreas, kidneys and adrenals. According to Ahvenainen it is not possible to make a correct clinical diagnosis. There are, however, some symptoms which seem to be fairly constant in infants. In newborns a bleeding tendency with signs of fetal damage and, in some cases, hepatomegaly and splenomegaly are symptoms pointing to the possibility of inclusion disease. It is not known whether the inclusion disease might be the cause of the frequent prematurity of cases. Blood dyscrasias and jaundice may be the leading symptoms of inclusion disease during the first two months of life In later infancy and early childhood inclusion disease may cause a variety of symptoms and a clinical diagnosis is impossible. Some cases show symptoms of the gastro-intestinal tract, others may have a pulmonary tract infection or symptoms of renal damage. Many of these patients do not gain weight satisfactorily and are anemic. According to Ahvenainen, the disease may be transmitted from the mother to the fetus during intrauterine life. The mother usually has no symptoms that could point to inclusion disease. The generalized infection or dissemination of the virus from the salivary glands may occur later It is not known which factors produce this dissemination and why the disease is so peculiar to infants and children. Some observers have found that disturbances of metabolism may be related to the dissemination of this disease in older children.

Bacala and Burke reported a case of generalized cytomegalic inclusion disease in a ten week old infant who died 79 days later. They emphasized that the clinical picture of this case, like most of the reported cases, was as protean as it was bizarre in its inclusion body distribution. There were

dermatologic findings, gastrointestinal disturbances, cerebral symptoms, respiratory difficulties, renal and adrenal involvement while cytomegalic inclusion-bearing cells were found in the skin, alimentary tract, brain, lungs, kidneys and adrenals respectively. The chronic eczema of this patient since the age of one month, the persistent diarrhea, the respiratory element in the picture, the cerebral signs, the renal and adrenal component unabated in spite of treatment, may well be explained by the involvement in each system. Apart from many lesions, the heart muscle showed areas of basophilic staining necrosis infiltrated with owl-eyed cells, lymphocytes, monocytes, and, very occasionally, with neutrophils. In addition to this granulomatous reaction, there were several of the large inclusion-bearing basophilic-staining cells found either between the myocardial fibres or actually separating the cytoplasm of the cell so that the cross striations could be followed around the inclusion-bearing cell but not through it. In this case, there was also remarkable thymic localization, interstitial pneumonitis According to Bacala and Burke, local signs and symptoms either directly due to viruses or as a reaction of tissues to the cytomegalic, inclusion-bearing elements were present in most cases. Whether or not related to the cause of death, they were in all probability related to the clinical course and picture of the disease. Clinical forms of the disease depend upon the predominant system chiefly affected by these viruses or by the presence of these abnormal owl-eyed giant cells.

The respiratory form has been present in a variety of pictures, especially as interstitial pneumonia. Dyspnea, cyanosis, x-ray findings, râles, mucoid or bloody expectorations have been the usual findings. Gallager, Stayman and Barba reported on a case associated with pulmonary cysts following an episode of pneumonitis shortly after birth. These cysts were treated by surgery and cytomegalic inclusion bodies bearing cells had been found in the excised lung tissue The occurrence of distinctive pneumonitis due to salivary gland virus was described in Wyatt, Simon, Trumbull and Evans Biopsy of the lung permitted the diagnosis to be made during life. The cerebral type presents a variety of central signs and symptoms (Kinney; Worth and Howard, Wyatt, *Saxton, Lee and Pinkerton, Kidder*, Fetterman).

The gastrointestinal form shows frequent colitis pancreatitis. The dermatologic type presents eczema, purpura, petechiae, ecchymoses, conjunctivitis The renal involvement was in the form of nephritis, hematuria, etc. Fetterman diagnosed this disease by urine examination and smears.

An adrenal form, a hepatobiliary form (jaundice, liver fibrosis, cirrhosis, necrosis etc.) and splenomegaly has also been described. The contributory findings of thymus and cardiac involvement have added to the severity of the cases, and to the poor prognosis. The diagnosis is based on the histopathology; symptomatic treatment is the rule.

A third case of salivary gland viral carditis has been reported by Worth and Howard and more extensively by Berton. This case was a six week old white male. The patient was a full-term, spontaneously delivered child. The infant had transient jaundice at birth. At the age of three weeks the patient started having diarrheal stools. On admission to hospital the infant was moderately dehydrated and had fever and rapid pulse. Excoriation of the skin of the buttocks and scrotum as well as a macular rash all over the head and forehead was noted There was hepato- and splenomegaly. The patient died on the second hospital day. There were numerous microscopic lesions in organs and tissues of the infant Inclusion-bearing cells resembling those of inclusion body disease of the salivary gland type were demonstrated in the brain, bone marrow, sweat glands, pituitary gland, lungs, spleen, adrenal, epididymis, testes and heart Inclusion bodies were present in the blood vessels, throughout practically all organs. The involvement apparently accounted for the numerous small hemorrhages and for the cerebral hemorrhage which was interpreted as the immediate cause of death by Worth and Howard.

Since the histopathologic character of the cardiac lesion of this case was not emphasized in the original report, Berton described the myocardial lesions which he regarded as of special significance. The myocardium showed scattered focal lesions characterized by progressive replacement of extensively altered muscle fibre by a loose, fibrillar to relatively compact connective tissue. A moderate to minimal cellular infiltrate with a degree of edema was also present Tinctorial changes accompanied by loss of cross striation and occasional moderate increases on width of certain of the myocardial fibres could be seen. In those fibres containing the typical intranuclear inclusion bodies a relative increase in size and peculiar bird's eye or owl's eye configuration of the nuclear structure was a constant feature At the same time, however, endothelial cells, especially those of small vessels, became parasitized In these cells the cytomegaly was striking. Many authors emphasize that the recognition of the disease is entirely dependent upon histopathology i e the finding of lesions where typical viral inclusion bodies are demonstrable. Only urinary studies and smears had up to the time been a laboratory aid of proved validity.

The identification in the heart of the etiologic agent producing the lesions as reported by Berton was accomplished solely in the finding of the "inclusion bearing cells." The other characteristics of the myocardial lesions are considered to be secondary to degeneration of the parasitized muscle fibres and to healing by fibrosis which follows. Berton suggested that his case of "salivary-gland virus carditis" might have been an infection of unusually high virulence by a variation of the salivary gland virus. Studies of Rosenbusch and Lucas showed that variations in virulence may be genuine in salivary gland virus disease of guinea pigs.

The salivary gland virus needs further investigations as it may throw light especially on the latent presence of virus in the body without symptoms of disease (Seiffert, Ahvenainen). But, on the other hand, there is increasing incidence and frequent generalized involvement in infants and children and occurrence in adults. In view of the prevalence of the cytomegalic elements in organs other than the salivary glands, the notion of salivary glands in the original terminology should be dropped and the disease should be called cytomegalic inclusion disease. The involvement of adults nullifies the "of infancy" pertinence to its first name.

Bacala and Burke observed in their case the presence of two varieties of lesions: (1) granulomatous in nature as exemplified in the myocardium and suggested slightly in the pancreas, (2) infiltration of other organs by large inclusion-body bearing cells without any reaction at all. While this could be explained on the basis of age of the lesion there is also a possibility of the pathogenicity of the invading agent or of the tissue reaction to its invasion (Bacala and Burke). The demonstration of specific inclusion bodies in the vascular endothelium suggests a widespread vascular damage. According to Hartz and van de Stadt there are in association with the inclusion body-bearing cells, typical inflammatory changes of the blood vessels which can perhaps be ascribed to the same causative factor. The inflammatory changes in the blood vessels are only found in the area containing the inclusion body-bearing cells and these cells are often observed in the inflamed vessels.

It is understandable that this vascular damage leads to increased capillary permeability, subsequent transudation and perhaps sometimes to circulatory collapse and death. In severe cases of generalized cytomegalic inclusion disease the capillary syndrome may be conspicuous. This syndrome may produce intersitial pneumonia, cerebral hemorrhages, purpura, petechiae, ecchymoses of the skin, structural alterations of kidney, liver, pancreas, heart and other organs. Such a development may add to the

severity of cases. Knowledge of the localized, generalized, symptomatic, fatal infantile and adult cases is still incomplete. It is hard to obtain definite knowledge of the course and the localization of lesions and, therefore, the treatment of the disease is difficult. The working hypothesis of the capillary syndrome as a cause of both clinical and anatomic phenomena of the cytomegalic inclusion disease may be useful for the direction of future management of the disease. In some cases plasma and whole blood seemed to have brought at least a transitory improvement.

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CHAPTER VI

Liver Diseases

Hepatitis A and B

Hepatitis may be produced by a series of viruses; it may be caused by infectious mononucleosis or by poliomyelitis. The main diseases referred to as "virus hepatitis" are infectious hepatitis, or hepatitis A, and the serum (homologous) (inoculation) hepatitis or hepatitis B. According to McCallum, these hepatitis viruses differ in their incubation period, apparent site of multiplication, routes of infection, common modes of transmission and immunologic behavior Observations of both natural infections and experimentally induced infections in human volunteers have showed that infectious hepatitis (A) and serum hepatitis (B) are different entities despite their identical clinical and histological manifestations (Stokes). Important is the antigenic distinction between hepatitis A and B. The skin test has proved that hepatitis virus A may have simple uniform antigenic properties similar to measles or mumps virus, in which one attack gives immunity and for which antibodies remain in the blood during life On the other hand, the information is incomplete concerning the unity or multiplicity of antigen types of viral hepatitis B (Stokes).

Hepatitis A has a fecal-oral type of spread whether epidemic or endemic, and this includes water, food and milk-borne epidemics. In viral hepatitis of the early neonatal period of infants a transplacental transmission is assumed In hepatitis B the causative agent is introduced directly into the bloodstream. The incubation period of hepatitis A is 20 to 40 days; of hepatitis B from 60 to 120 days.

Viral hepatitis presents two distinctive phases following the incubation period, the anicteric and the icteric stage of the illness. The diphasic course is often reflected in a two-peaked type of temperature curve. The first phase during which the internal organs show no obvious alterations, lasts three to five days and may often be followed by recovery. In the icteric stage the level of temperature bears no relation to the severity of the hepatitis. The liver is more or less enlarged; there may be splenomegaly Oliguria develops which grows into polyuria as soon as the climax of the disease is passed.

Viral hepatitis often shows various symptoms and signs of a diffuse disease: tracheo-bronchitis, pneumonitis, myocarditis, gastro-enteritis, nephritis, encephalitis, encephalo-myelitis, Landry-Guillain-Barré syndrome; the organ chiefly attacked is the liver. Viral hepatitis is usually cured within six to eight weeks but in ten per cent of cases, only after three months of illness. Few cases pass into chronic hepatitis, some of them may be still cured at a later date. A small part die from acute liver necrosis. The fatal issue depends on the character of the epidemics, i.e. the virulence of the causative agent and other factors such as age, previous starvation, pregnancy, wounds, infections and hyperthyroidism.

When jaundice appears in older children and adults, a large part of the liver may be already destroyed but at the same time a greater or lesser degree of regeneration has taken place in the liver. Heart involvement in virus hepatitis has been observed by pathologists Siegmund observed only slight interstitial edema of the heart in fatal cases of viral hepatitis and found no myolysis or interstitial cell infiltration Loeffler reported 14 fatal cases from viral hepatitis and observed cardiac changes in 6 patients (dilatation of the whole heart, particularly of the right ventricle and auricle, hypertrophy of the right ventricle, dilatation of the auricles, focal fatty degeneration or brown atrophy of the myocardium). Junet and Alphonse found perivascular cell infiltration of the heart muscle and fatty degeneration of myocardial fibres Wood reported, in a case of fulminant viral hepatitis, myocarditis characterized by interstitial lymphocytic and mononuclear cell infiltration. But myocarditis may also develop in the subsiding phase of non-fulminant viral hepatitis Because of the rarity of histological observations a case of this type may be described here in a little more detail. (I am indebted to Prof J. Kleeberg, Internal Dept A., Hebrew University Medical School and Prof H Ungar, Dept Path Anat and Histol., Hebrew University Medical School, for their cooperation and courtesy in permitting study and publication of this case)

Mr. M C , 23 years, from New York, had been in Jerusalem as a visitor He was infected with infectious hepatitis and died 15 days after onset of the disease in a state of coma The urinary output decreased at the onset of the disease and progressed to anuria Erythrocytes, four days before death, were 5,410,000, hemoglobin 14 Gm per cent, two days before death erythrocytes were 3,610,000, hemoglobin 10 2 Gm per cent and thrombocytes 179,000 Leucocytes, six days prior to death, 5,600, two days later 10,200 and one day before death 14,300.

Blood urea was 195 mg per cent four days before death, 380 mg per cent one day before death. Serum bilirubin were 30 mg per cent and glucose 132 mg per cent four days before death. On the same day, Thymol turbidity was 15 Thymol turbidity flocculation ++,

Dilution turbidity test 16 8, Welt-
Cephalin +++, Alkaline phosphatase 6 8 Bodansky U. Dilution turbidity test 16 8, Welt-
man 9 Three days before death total plasma protein was 5 95 Gm. per cent, albumin 3 8 Gm.
per cent, globulin 2.15 Gm. per cent. Alkali reserve, four days before death was 50, the follow-
ing day, 28 7, the day after that 27.1 volume per cent Serum calcium, four days before death
was 9 9 mg per cent and serum sodium in the last three days of life 310, 140, 142 mg. per cent
respectively There were blood pressure recordings between 115/80 and 100/60 mm Hg during
the last days of life An electrocardiogram five days before death showed a heart rate of 144,
sinustachycardia, slight depression of ST in leads I, V_4, V_5, V_6 and AVF. T waves were almost
absent in lead I and showed a late positive rise in leads II, III. T waves in V_2, V_3, V_4 were
upright and in V_5, V_6 absent. T waves were also absent in unipolar extremity leads. The QT
time, although not exactly measurable, seemed considerably prolonged. The electrocardio-
gram was strongly suggestive of myocardial damage.

Necropsy Diffuse hepatitis in the subsiding phase of viral hepatitis (according to Smetana,
Keller and Dubin), regeneration of parenchymal cells had progressed to a remarkable degree.
Some postnecrotic collapse of the periphery of the lobules was present. There was portal
infiltration and lipochrome pigment in the Kupffer cells Slight icteric nephrosis. Jaundice.
Heart one focus of fibrosis and inflammation was present in the vicinity of the anterior de-
scending coronary artery, extending deeply into the ventricular wall. The infiltration was
chiefly composed of lymphocytes The area involved showed loss of muscle fibres, and an ap-
parent increase of connective tissue, only one such focus was seen Obstruction of small pan-
creatic ducts and acini. Chronic cholecystitis Splenomegaly, hemorrhage into the gastro-
intestinal tract Cerebral edema Hyperplasia of bone marrow, pulmonary atelectasis, em-
physema and pneumonia Signs of blood aspiration. Chronic bronchitis.

Other fatal cases of viral hepatitis showed subendocardial and epicardial hemorrhages.

In clinical descriptions of the course of this jaundice, the presence of bradycardia and hypotension is stressed and the occurrence of circulatory lability is frequently mentioned Schennetten shows that patients suffering from viral hepatitis have bradycardia in the recumbent position and an increased cardiac rate and reduced pulse pressure on transition from the recumbent to the erect state Hemodynamic alterations in hepatitis in correspondence to the damage of blood and lymph passages in the liver have been emphasized in Part I Alterations of the capillary permeability, loss of plasma from the circulation are responsible for a reduced circulating blood volume (hypovolemia) Edema of the legs and ascites occurring in viral hepatitis are partly caused by hypoalbuminemia. Changes in hemodynamics are the reason for fatigue and adynamia in hepatitis patients Since sitting and standing cause a further reduction in the active blood volume, a corresponding electrocardiogram indicates an insufficient coronary blood flow (Wollheim) Adler and Lyon drew attention to the tiredness, inclination to dizziness and angina-like heart symptoms in

hepatitis A, all these symptoms extending into the period of convalescence. In some electrocardiograms described there were alterations in form and level of ST segments and T waves during rest and after effort.

The evaluation of electrocardiographic findings during the active period of viral hepatitis meets with difficulty since—as has been pointed out by Meier—in 80 per cent of icteric cases, lowering of the ST segment and flattening of the T waves may be present. These are, however, likely to disappear as soon as jaundice subsides or even a few days earlier. They are probably produced by the action of bile acids on muscle fibres. The resemblance of these electrocardiographic changes caused by jaundice with those appearing after the administration of cardiac glycosides is explained by the chemical relationship between these substances All cardiac glycosides contain the cyclopentanoperhydrophenatren structure which is also present in the bile acids.

Louis reported various electrocardiographic alterations—T and ST segment changes and arrhythmias in 24 out of 47 cases which were however due to toxic and incretory factors Hoagland and Shank mentioned cardiovascular disturbances, particularly abnormal cardiac rhythm and prolongation of PR interval, in this disease.

Dehn, Feil and Rinderknecht noted, in nine students suffering from hepatitis, flattening of T waves; these alterations were explained by myocardial alterations

Adler and Lyon made a detailed study of cardiovascular involvement in 8 out of 150 cases All patients developed subjective and objective cardiac symptoms, part of them during the acute stage of the disease, others immediately afterwards and still others after a long interval during which the patients had already resumed their usual activities. There were palpitations, slight dyspnea, particularly on effort, a troublesome oppression on the chest, anginal pain, occasionally radiating into the left arm, dizziness, lassitude, weakness. Change of size of heart in any considerable degree and abnormal auscultatory findings were occasionally encountered. The pulse was now and then poorly filled, in seven cases accelerated. The blood pressure was often low, and extrasystoles were frequent Electrocardiographic alterations included prolongation of PR, prolongation of QRS, notching of QRS, changes of P, ST, alterations of T waves, disturbances of rhythm In severe cases there were high T waves, sometimes accompanied by bradycardia. In a number of cases the QT was prolonged. The electrocardiographic changes were either transient or persistent. The

prolongation of QT duration (Hegglin, Adler and Lyon; Mettler, Junet and Alphonse, Schennetten) in infectious hepatitis was interpreted as a cardiac-energetic insufficiency (Hegglin). According to Lyon, early in the icteric stage of the disease, there is no prolonged QT, even in severe cases. It takes some time to develop, and is then found in less severe cases later in the icteric phase and after jaundice has subsided. It was not always distinct in cases with hepatic coma. QT prolongation was absent in cases with slight bilirubinemia that persisted for months as the only finding in some cases after viral hepatitis. QT prolongation could sometimes be demonstrated for a few days only but sometimes also for some weeks and occasionally for years. In some cases the QT prolongation is associated with shortening of the interval Q- second heart sound, i.e. in cases of energetic-dynamic cardiac insufficiency (Hegglin). The QT prolongation in viral hepatitis is a disturbance of the cardiac metabolism; pathologic alterations of plasma proteins and electrolytes are involved leading to functional and reversible and occasionally to anatomic and irreversible alterations.

Hypokalemia occurring in severe cases associated with liver cell failure may lead to electrocardiographic changes and perhaps to hypokalemic myocarditis. Myocardial and electrocardiographic alterations, observed in severe viral hepatitis, may have a metabolic component—more frequently than formerly assumed. Hypalbuminemia or dysproteinemia in acute and chronic viral hepatitis may lead to "myocardosis" (Wuhrmann). Prolonged hypoglycemia may also accompany viral hepatitis and may extend into the period of convalescence (Lyon)

Hypoglycemia may also play a role in alterations of the cardiac metabolism (Schennetten). The fall of serum albumin in viral hepatitis is important because the osmotic equilibrium is mostly controlled by the albumin molecule. Schennetten found in the electrocardiograms of five out of 12 patients, a low voltage R and flat T waves and assumed that these alterations were caused by a hydropericardium. Electrocardiographic changes in viral hepatitis may be produced by *myocarditis*, *by hypovolemia* associated with insufficient coronary blood flow, *by metabolic disturbances* (hypalbuminemia or dysproteinemia, hypoglycemia, hypokalemia, jaundice) by hydropericardium and by autonomic imbalance as observed in many infectious diseases.

Observations of cardiovascular involvement have been made to a great part in hepatitis A but hold also for hepatitis B. The *frequency* of hepatitis

B has increased with the advancement of the whole blood and plasma therapy. It is a serious disease and its course unpredictable.

The therapy of cardiac involvement in viral hepatitis is identical with the present-day treatment of viral hepatitis. *Rest in bed and good nursing* are essential. The restitution of euproteinemia is necessary. To give the patient sufficient protein is more important than the earlier carbohydrate diet. A diet poor in protein results in a superimposed nutritional deficiency augmenting the depletion of serum albumin, caused by the toxipathic action of the hepatitis virus on the liver. The intravenous administration of plasma as early as possible prevents further depletion of body proteins, may protect the liver, kidneys and the central nervous system. Blood and/or plasma infusion and/or blood substitutes (Periston, Periston N, Plasmosan, dextran) may restore the osmotic pressure, keep away peripheral collapse by correcting the progressive loss of an active blood volume. Plasma administration in the early stage of not too severe hepatitis is likely to restore euproteinemia Withdrawal of protein before, during or after hepatitis may give rise to secondary metabolic disturbances of the heart and other organs Even in severe cases of hepatitis early *administration* of plasma plus a continuous drip of glucose and NaCl solution combined with transstomachal glucose is often followed by an increase of total serum protein and of its albumin fraction, and depression of globulin fractions. Fluids and protein diet should be started as soon as possible. Protein deficiency persisting for some length of time must make itself felt long before the drop in plasma protein by a protein disturbance of the liver cells reducing its resistance to toxic effects A patient taking a diet deficient in protein for long periods of time may have nitrogen equilibrium if energy requirements are met by carbohydrates and fat, but the patient has no reserves for illness Thus, an insufficient protein intake may delay cure of viral hepatitis and its complications.

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CHAPTER VII

Neurotropic Virus Diseases

1. Viral Encephalitides and Encephalomyocarditis

The pathogenesis of viral encephalitides in man is almost unknown. In some of the human encephalitides a diphasic type of infection occurs. It is assumed that during the first phase the virus circulates in the blood and in the second (the neural) phase no viremia is present but it is then that neurologic disturbances occur. The lack of cross-immunity appears the most important criterion for distinguishing viral encephalitides.

Epidemic encephalitis (encephalitis lethargica or von Economo's disease) is probably a viral infection According to van Rooyen and Rhodes, encephalitis lethargica bears many of the characteristic stamps of a viral infection although no specific virus has yet been generally accepted as the causative agent There is no question that the virus of herpes simplex can cause an encephalitis that resembles encephalitis lethargica in many ways. But it is highly probable that von Economo's original encephalitis was not produced by herpes simplex virus The causative agent of epidemic encephalitis is unknown. Epidemic encephalitis is characterized by alterations in the grey matter of the brain and the basal ganglia The lesions are degenerative and inflammatory in nature Many viral encephalitides, transmitted from animal to man are reported from different parts of the world: St. Louis encephalitis, Japanese B encephalitis, a series of equine encephalitides (all spread by mosquitoes) tick-borne, Russian, spring-summer, and louping ill The mosquito-borne encephalitides are closely related to dengue and yellow fever, but in the mosquito-borne type the main part of the cycle of survival is in non-human hosts (Burnet) They show many extrapyramidal and less pyramidal symptoms, and may be associated with mental disturbances

Lymphocytic choriomeningitis is a generalized systemic infection with a primarily meningotropic virus which not infrequently becomes pneumotropic and neurotropic (Colmore) In lymphocytic choriomeningitis mice are the probable source of human infection

Recently some African viruses have been found to be neurotropic in laboratory animals. In humans, West Nile virus infections have been ob-

served. This virus is antigenically related to St. Louis and Japanese B virus. In Israel the virus has been isolated during small epidemics of a definite clinical character in 1951, 1952, and 1953. The main symptoms of the disease were fever, severe headache, aching of the back and the limbs, swelling of lymph nodes, a rash, abdominal pain and vomiting. Pathological reflexes pointing to an involvement of the central nervous system have also been observed. Recovery is complete and no sequelae of the disease have been seen up till now. The diagnosis was made by isolation of West Nile virus from patients and by the demonstration of a rise of antibodies during the disease. The infection is apparently transmitted by *Culex molestus* (Bernkopf).

It appears that some as yet unrecognized viruses may cause one form of inclusion encephalitis which has in some cases been proved to be due to herpes simplex Cases of subacute inclusion encephalitis bear a very close resemblance to subacute sclerosing encephalitis.

Foley and Williams emphasize that subacute infections of the nervous system may have much greater importance than is inferred from their rarity. The recognition, by Dawson, of subacute inclusion encephalitis and the description by van Bogaert of the closely similar condition, subacute sclerosing leucoencephalitis have made it clear that these conditions which on histological grounds are almost certainly of viral origin, may run a course resembling in many respects that of progressive diseases hitherto regarded as degenerative Now we have come to suspect that a virus infection can produce a subacute or chronic syndrome of clinically recognizable, severe encephalitis associated with electrocardiographic changes indicating myocardial damage and/or sudden unexpected death.

Viral encephalitides comprising a stage of generalization may lead to cardiac manifestations of the disease. In experimental and human viral encephalitides, cardiovascular involvement has frequently been observed. The term "encephalomyocarditis" which emphasizes the significance of the central nervous system and the myocardium, today signifies a certain family of viruses with viscero- and neurotropic properties.

But apart from the experimental or human disease caused by these viruses, a clinical and pathologic entity has been described, consisting of clinically recognizable evidence of severe encephalitis combined with electrocardiographic changes indicating myocardial damage and often unexpected death. The involvement of either the brain or the myocardium may not be recognized until convulsions and coma appear, followed by

unexpected death. Such instances were described by Saphir and other authors; a viral etiology in these cases was assumed but not proved.

Other virus diseases may occasionally produce acute meningitis and/or encephalitis and/or myelitis and radiculitis; these manifestations of nervous system involvement are observed during the course of mumps, infectious mononucleosis, measles, rubella, influenza, chickenpox, herpes simplex, herpes zoster, psittacosis, ornithosis, lymphopathia venereum, cat-scratch disease, variola, viral hepatitis, atypical pneumonia and Coxsackie infections. In some diseases the mechanism is considered to be allergic (wrongly or rightly). Instances of damage of the nervous system during viral diseases occur more frequently than it is generally assumed. Viral maladies causing a stage of generalization (viremia) may lead to manifestations within the central nervous system and sometimes, simultaneously, within the heart. In such cases a clinical syndrome of "encephalomyocarditis" may develop which indeed can be produced by different viruses that only rarely have neurotropic plus viscero- (cardio-) tropic properties operating at the same time

The viral encephalomyocarditis group comprises related viruses of the so called encephalomyocarditis or parapoliomyelitis family which have obvious viscero- and neurotropic properties They have a tendency to produce inflammatory changes in the heart of rodents. They comprise the encephalomyocarditis (EMC) virus (Helwig and Schmidt, Schmidt), the MM virus (Jungeblut and Schmidt), the Columbia SK (Col SK) virus (Jungeblut and Sanders, Jungeblut and Steenberg), and the Mengo virus (Dick). Other representatives of the family are Lt 23 virus (Beller and Keller), F and Senger virus (Bieling and Koch), Ortlieb virus (Vivell, Verlinde and Hofman). These viruses which are named parapoliomyelitis viruses, were isolated from human poliomyelitis-like cases, or from human beings suffering from a disease which presented a variegated symptomatology including encephalomyelitis and myocarditis The experimental work, reported by Helwig and Schmidt, Schmidt, was based on a virus, primarily isolated from a five year old chimpanzee, dying from myocarditis, then from guinea pigs with myocarditis and from mice and hamsters with myocarditis plus paralysis, myelitis and encephalitis Intensive focal myocardial necrosis was found when the illness ran a prolonged course. This virus had not been identified with any of the variations of known viruses by biological tests. Helwig and Schmidt found that the cardiac lesions of this chimpanzee and sporadic human acute interstitial myocarditis of unknown etiology were strikingly identical. Warren and

Smadel have maintained this virus by intracerebral inoculations in mice and found it highly neurotropic. The agent was quite potent when inoculated whether intraperitoneally or intracerebrally in extreme dilutions. Warren and Smadel did not observe myocarditis in the rapidly dying animals, but extensive focal necrosis was found when the illness ran a more prolonged course. These authors named this virus encephalomyocarditis (EMC) virus.

Meningoencephalomyelitis, encephalomyocarditis, Columbia SK and MM viruses are closely related seriologically and in their pathogenicity and their pathological effect on experimentally infected small laboratory animals (Dick).

Much confusion has been caused by the use of the names "Columbia SK and MM murine strains of poliomyelitis." Since it has been shown that these viruses bear no antigenic relationship to the strains of poliomyelitis virus and since they are closely related, serologically, to Mengo and EMC viruses, Dick suggested that the word poliomyelitis be dropped from the names Since EMC virus is indistinguishable from Mengo virus and myocarditis is not a specific lesion characteristic only of their group *the name encephalomyocarditis is also unsatisfactory.*

Warren, Smadel and Russ found, by means of neutralization complement fixation and cross-immunity tests, that the viruses of encephalomyocarditis, Columbia SK, MM and *Mengo-encephalomyelitis are identical*, analysis of their known physical and pathogenic properties further indicates that they are probably different strains of a single virus.

During the winter of 1945/46 a febrile illness designated as aseptic meningitis or three-day fever occurred in Manila. Smadel and Warren were able to demonstrate high antibody levels (neutralization indices above 1000) to EMC virus in seven persons who had suffered from this three day fever All patients recovered quickly, *no* signs of cardiac disease or other sequelae were observed

Mengo-virus has been isolated from the mongoose, rhesus monkeys and mosquitoes and appears to be infectious for *men*

Jungeblut and Steenberg found that, in mice infected intraperitoneally with Col SK or EMC virus which has been harvested from spleens of infected mice and carried as a *splenic strain over* ten passages, paralysis is associated with myocarditis Specific antibodies for Col SK and YSK virus could be observed in patients who had experienced paralytic and non paralytic poliomyelitis (Jungeblut).

Kalm examined the central nervous system of 22 monkeys which had

been infected intracerebrally, intraperitoneally and intramuscularly with Col SK, F and Ortlieb viruses in the laboratories of Jungeblut (New York) and Verlinde (Leyden) and found that the three viruses produced alterations not identical with the changes induced by human poliomyelitis.

Gaedeke stressed the immunobiologic similarity of the EMC (parapoliomyelitis) group of viruses and their obligate pathogenicity for adult mice. Alterations of tissues of infected mice are encephalomyelitic reactions, lesions of myocardium, alterations of skeletal muscles and peripheral nerves. The cardiac manifestations are a part of the pathologic picture caused by the EMC (parapoliomyelitis) viruses. The coincidence of parapoliomyelitis infection with myocarditis was described by Koch in a human case; a virus (F strain), positive neutralization test and the histologic findings of myocarditis were demonstrated. In subacute cases of the same infection electrocardiographic alterations have been observed (Koch). According to Bieling, Bieling and Koch, such viruses have been rather common in the neighborhood of Giessen and Marburg in Germany. Bieling and Koch reported 12 cases of abacterial meningitis caused by this virus of the EMC group. These authors found that rats in the neighborhood of human cases had neutralizing antibodies in the serum while controls did not have them The vector from rat to man may be a mosquito (Culex pipiens).

Warren, Russ and Jeffries found that approximately 20 per cent of wild-caught rats, trapped in various portions of the United States, possessed considerable neutralizing antibodies against the viruses of the EMC group In contrast, the finding of antibodies against EMC virus in human beings is less frequent. Excluding the Manila series, Warren, Smadel and Russ examined over 300 human sera for neutralizing antibody against EMC virus and only 9 were positive. Three of the 9 positives were from cases diagnosed as mild aseptic meningitis on clinical grounds; one was from a 23 year old nurse complaining of mild upper respiratory symptoms and headache and the remaining were from patients with a diagnosis of a mild or non-paralytic poliomyelitis. None of these nine patients had signs of cardiac disease and all eventually recovered.

Schmidt suggested that "isolated myocarditis" may be caused by a virus similar to that of the EMC group. Koch, Bieling also assumed that isolated interstitial "idiopathic" myocarditis of infants may be produced by a virus of the EMC group. However, the role of this causative agent in Fiedler's myocarditis remains a matter of speculation. Warren, Smadel

and Russ found no neutralizing antibodies against EMC virus in nine cases of primary idiopathic myocarditis of Fiedler's type.

Pathohistologic descriptions of experimental infections in mice injected with EMC (parapoliomyelitis) viruses resemble the pathologic picture of cases of human poliomyelitis (Burrows, Hellmann; Sommers, Wilson and Hartman, Wolmann and Liban). According to Gaedeke, clinical poliomyelitis is a syndrome of different etiology. There are some diseases of man and animals which have similarities to human poliomyelitis or have features in common with poliomyelitis. The earlier conventional concept of poliomyelitis as a strictly neurotropic infection has been challenged. Damage of extraneural substrates frequently occurs and the heart muscle is affected in a considerable number of cases of genuine human poliomyelitis

In epidemic, lethargic encephalitis cardiovascular involvement has rarely been reported. Paroxysmal tachycardia and some electrocardiographic abnormalities have been mentioned and have been interpreted as being caused by nervous disturbances of central origin. According to von Economo, as a matter of fact, in exceptionally severe cases myocardial degeneration may supervene. Ungar (1948) described a diffuse interstitial myocarditis in a 65 year old man suffering from epidemic encephalitis. Histologic studies of the brain revealed perivascular infiltrations showing the character and distribution to be typical of acute epidemic encephalitis. The almost complete absence of lesions in the medulla oblongata, the rarity of neuronophagia and the absence of polymorphonuclear leucocytes within the infiltrations was taken into account in a differential diagnosis against polioencephalitis.

In the heart, myocardial infiltrations of small round cells were the only pathologic change to be observed. No significant pathologic alterations other than the encephalitis were associated with myocarditis. In approximately fifty per cent of the cases of epidemic encephalitis the degenerative cerebral changes were associated with fresh inflammatory encephalitic lesions. Virus diseases of the nervous system usually run an acute course. Although it is recognized that the sequelae of epidemic encephalitis may last many years, it is only in recent years that it has been suspected that a virus infection can produce a subacute or chronic, progressive condition. In chronic cases of epidemic encephalitis, paroxysmal tachycardia is no rare event. We suspect that the causative virus may persist to parasitize

the cells of the nervous system and the heart for many years after the initial attack.

Kuhn (1948) described the clinical and especially the electrocardiographic changes in cases of lymphocytic meningitis which were found during an epidemic in Zurich during the summer of 1948. While a viral infection was assumed it could not be decided whether it was a meningitic form of poliomyelitis. Kuhn reported auricular extrasystoles, flattening of T waves in all leads. It was not possible to determine whether these changes were caused by infectious-toxic myocardial damage or by an interstitial myocarditis produced by focal inflammation within the auricle. Schildknecht (1953) reported from Switzerland cases of encephalomeningitis lymphocytaria which affected the skin, liver, kidneys and in an additional case, the myocardium.

Hloucal (1953) described the outbreak of arthropod-borne virus encephalitis in Czechoslovakia. Several types could be distinguished: meningoencephalitis, meningitis, encephalomyeloradiculitis, and abortive cases. In two cases transient myocardial damage was found.

In Russian Far East encephalitis parenchymatous degeneration of the liver, kidney and heart has been mentioned

Encephalomyocarditis as a "Clinical and Pathologic" Entity and as a "Clinical" Syndrome

Saphir described encephalomyocarditis as a clinical and pathologic entity, Brenning as a disease *sui generis*. In such cases unsuccessful attempts, or no attempt at all, were made to isolate a virus of the encephalomyocarditis group.

Brenning reported three clinical observations on encephalomyocarditis stressing a rather sudden onset with marked anxiety, reflex disorders with or without involvement of cranial nerves, and simultaneous marked subjective heart trouble with more or less pronounced circulatory insufficiency.

Richdorf observed myocardial failure with brain involvement in children; in one instance subacute encephalitis with electrocardiographic changes.

Saphir reported three cases of simultaneous myocarditis and encephalitis. The patients were 52, 35 and 13 years of age The course of the disease in two of the three patients was rapid, one dying after only eight hours' hospitalization and the other at home after a short history of headache

and fever. The first patient was hospitalized 13 days prior to her death. All three patients had the type of encephalitis usually ascribed to a viral origin. A clinical diagnosis of encephalitis was made in the first and third instances, but was not made in the second, the patient having died at home. Myocarditis was diagnosed, clinically in one cases only, but was found at autopsy in all three. Though morphologically the myocarditis *per se* is not characteristic in these instances, it resembles that seen in certain stages of poliomyelitis and also in the two chimpanzees observed by Helwig and Schmidt and Schmidt. In spite of the inability to demonstrate a virus it seems likely that both the encephalitis and myocarditis were caused by a virus and most likely that the cause of the encephalomyocarditis was a virus of the encephalomyocarditis virus family.

Betke and Harms described the coincidence of diffuse encephalomyelitis and severe myocardial damage in nine infants and children observed during a period of one and a half years A viral etiology was assumed in these cases The clinical syndrome of encephalomyocarditis is considered not a rare occurrence In two of these cases there had been vaccination, in one chickenpox, in another viral hepatitis, in others influenza prior to the disease These viral infections may have produced the encephalomyocarditic syndrome, but a uniform virus as the causative agent could not be excluded.

Saphir recommends whenever such a disease complex is considered clinically that the serum be examined for neutralizing antibodies involving the viruses of encephalomyocarditis, the meningoencephalitis virus, the Columbia SK and MM viruses At autopsy an attempt should be made to isolate the virus from the heart and brain by the inoculation of mice, hamsters or chick embryo

Although viruses belonging to the encephalomyocarditis family and also poliomyelitic viruses possess more pronounced neurotropic plus viscero(cardio)tropic properties than other viruses, simultaneous encephalitis and myocarditis may be produced by various viruses In these cases encephalomyocarditis is regarded as a clinical syndrome. Instances of mild cerebral and cardiac complications in virus diseases are being frequently overlooked The patients often recover completely or may have some neuropsychic sequelae and/or persistent minor electrocardiographic abnormalities. Severe and fatal sequelae, produced by encephalitis or by myocarditis or by both in viral diseases are occasionally observed. Some

examples seen in different infections of true or probable viral origin may be mentioned in greater detail.

Infectious mononucleosis is a common disease of possible viral etiology. Allen and Kellner found, at necropsy, focal cellular infiltrations in the brain, heart, kidney, lungs, adrenals and testes. Histologic studies of the brain of this case which had no clinical symptoms directly referable to organic changes in the central nervous system revealed a picture similar to that seen in mild virus encephalitis. The infiltrations seen in the heart were compatible with conduction changes, demonstrable by electrocardiograms assuming that the infiltration may occur in any part of the cardiac muscle and may involve important conductive fibres.

We observed a 15 year old boy from March until December 1946. He obviously had infectious mononucleosis (Paul Bunnell test 1:160, 80 per cent mononuclear cells with many abnormal infectious mononucleosis cells in the blood) Six weeks after the onset of the illness he developed a lower motor neuroparesis and an acellular hypalbuminosis in the spinal fluid. The patient was suffering from headache, disturbances of vision, mental confusion, and was temporarily semicomatose. The boy suffered for 8 months, recovered, but some neuropsychiatric sequelae persisted. In this case there was flattening of T waves of some leads in the electrocardiogram, early in the illness, which later returned to normal. A second case was an 18 year old male patient with infectious mononucleosis, (lymphadenopathia, sore throat, splenomegaly, Paul-Bunnell test 1 640, 6000 leucocytes, 63 per cent mononuclears with 11 per cent abnormal infectious mononucleosis cells) observed during 1952 During the early course of the disease there was nuchal rigidity, headache, nausea, vomiting, somnolence, blurred vision and a positive Kernig sign for four days (meningoencephalitis). The first electrocardiogram showed SR = 0, 22", T_1 low, T_2 low, three weeks later an electrocardiogram revealed PR 0, 21", T_1 and T_2 taller The recovery from the central nervous system involvement was complete.

The simultaneous occurrence of the Landry-Guillain-Barré syndrome with completely developed polyneuroradiculomyelitis, very severe neurovegetative imbalance, circulatory and respiratory disturbances of a central type, myocarditis and high Paul-Bunnell titer and death are mentioned by Knick and Hoffmann The Landry-Guillain-Barré syndrome in infectious mononucleosis was associated with myocarditis demonstrable by electrocardiogram and histological findings (Klein) According to Custer and Smith, the cerebrospinal fluid findings in infectious mononucleosis are variable, most frequently they are normal, but the pressure is sometimes increased and a lymphocytosis of several hundred cells and an increase in protein have been observed. The differential diagnosis between infectious mononucleosis and lymphocytic choriomeningitis may be difficult. In

infectious mononucleosis a positive heterophil-antibody test may sometimes be obtained from the spinal fluid. Infectious mononucleosis should be considered as one of the causes of Landry-Guillain-Barré syndrome. It is important to have repeated Paul-Bunnell tests done in all cases showing the syndrome or other central nervous system involvement without apparent cause

Mumps meningoencephalitis with and without parotitis is, in certain years, a frequent form of lymphomeningoencephalitis among children and adults. Bland described a case of mumps associated with myocarditis, meningoencephalitis and pancreatitis.

Many authors regard viral hepatitis as a "generalized infectious disease" in which myocardial damage and encephalitis or encephalomeningitis accompanied by psychotic reactions during the course of illness occur. In fulminant viral hepatitis, but also in the subsiding phase of this illness, interstitial myocarditis has been observed. According to Wahi and Arora in spite of the frequent severe symptoms referable to the central nervous system in fulminant cases of viral hepatitis the histologic changes in the brain consisted only of swelling of ganglion cells with distortion of their nuclei In subacute fatal cases there was lymphocytic infiltration in the basal ganglions, in one case kernicterus was found in the lenticular nucleus, a rare occurrence in adults Streifler and Feldmann reported the case of a 19 year old girl who suffered from encephalomyelitis complicating the preicteric stage of infectious hepatitis; the case reported was probably the result of direct viral action on the central nervous system.

In 1944 we observed a boy aged 15 years with acute meningoencephalomyelitis and radiculitis occurring on the ninth day after the onset of a severe viral hepatitis It persisted for 10 days with violent pain in the back and in the small of the back while later there was retention of urine, sensory disturbances and increasing weakness of legs, prostration and mental confusion. There was no complete paralysis of extremities. Examination revealed flaccidity and abolishment of reflexes of the lower limbs. Cardiovascular involvement during the icteric period of the disease could not be excluded, but proper evaluation of electrocardiographic findings (depression of ST segments and flattening of T waves) during this phase was met with difficulties. Almost every case of jaundice may present such electrocardiographic abnormalities probably as an effect of the action of bile acids The patient recovered; there was no mental deficiency but symptoms of emotional instability persisted.

Parker, Jr., Joliffe and Finland found, in fatal cases of primary atypical pneumonia, lesions of the brain consisting of perivascular hemorrhages with some glial proliferation, few scattered large mononuclear cells, lymphocytes and plasma cells in the cerebral meninges. In cases of atypical pneumonia they recorded subendocardial hemorrhages extending into the adjacent myocardium with necrosis of a few heart muscle fibers or some interstitial myocarditis. We observed a woman of 72 with a primary atypical pneumonia of unknown etiology in the first part of 1952. During the course of the pneumonia an ascending and descending Landry-Guillain-Barré syndrome appeared; it was associated with sphincter paresis and development of bed sores which persisted for 12 weeks. Dysphagia was present. There was no permanent wasting of the affected muscles. In the early course of the disease the electrocardiogram showed inverted T waves in lead I and the outer chest leads. The T abnormalities lasted for five weeks. The patient recovered completely

Olitsky found the histologic picture of infectious polyneuritis, i e. the Landry-Guillain-Barré syndrome "somewhat similar to that observed in avian encephalomyelitis" Focal degeneration and necrosis associated with infiltrations of mononuclear cells may be present in the adrenals, heart and kidneys (Olitsky and Casals)

Other viral infections which mainly involve tissues other than the nervous system and the heart, may occasionally and simultaneously implicate the nervous system tissue and the myocardium. The encephalomyocarditic syndrome is almost regularly observed in severe rickettsial diseases, epidemic hemorrhagic fever and in acute toxoplasmosis.

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Other viral *infections* which *mainly* involve tissues other than the nervous system and the heart, may occasionally and simultaneously implicate the nervous system tissue and the myocardium. The encephalo-myocarditic syndrome is almost regularly observed in severe rickettsial diseases, epidemic hemorrhagic fever and in acute toxoplasmosis

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accompanied by interstitial edema in four of six patients dying from poliomyelitis Hertz, Johnson and Depree (1912) reported on a patient who recovered from an attack of infantile paralysis with optic neuritis and myocarditis of several months' duration.

In 1918 Abramson described perivascular collections of mononuclear cells in the connective tissue septa between normal myocardial bundles. Further brief descriptions of myocardial lesions *in poliomyelitis were given by* Cowie, Parsons and Lowenberg (1934) and Clark (1938). It was only during the last 12 years that pathologists started analysing systematically the morphologic changes of the heart observed in this illness. It was soon learned that myocarditis was a frequent manifestation in fatal cases (Saphir and Wile, 1942; Peale and Lucchesi, 1943; Dublin and Larson, 1943; Dolgopol and Cragan, 1948; Ludden and Edwards, 1949; Teloh, 1953; Fox, Sennett and Kuzma, 1953; and many others).

Myocarditis observed in poliomyelitis is exudative and chiefly limited to the interstitial tissues Interstitial edema was observed *in most of the hearts examined by Dolgopol and Cragan. In many cases this edema not* only involved the perivascular connective tissue but extended within the muscle bundles, between individual myocardial fibers. Interstitial edema may be severe (Fox, Sennett and Kuzma) Cardial involvement is often minimal, and focal in distribution, sometimes extensive. There may be focal infiltration of a small number of lymphocytes, plasma cells, macrophages and polymorphonuclears, but the cell infiltrations may be more numerous and extensive The lesions are most frequent in the posterior wall of the left ventricle and the posterior papillary muscle, also in the left auricle and interventricular septum (Dolgopol and Cragan). Intrasarcolemmal fragmentation of myocardial fibers with preservation of striated myofibrillae and collapse of sarcolemnal sheets was seen in cases in which there was no myocarditis and in a few cases of myocarditis (Dolgopol and Cragan) Endocardial lesions were described by Ludden and Edwards; Luhan; Weinstein and Shelokov The latter two authors described a case of acute pericarditis with a sterile creamy effusion that contained neutrophils and fibrin and extended into the superficial layers of myocardium. The occurrence of myocarditis on the second and third day of poliomyelitis and death from cardiac failure on the fourth and fifth day, indicate that myocarditis may be a very early complication taking place before bacterial invasion of the respiratory organs becomes sufficiently severe to lead in turn to focal myocarditis (Dolgopol and Cragan)

2. Poliomyelitis

Poliomyelitis (acute anterior poliomyelitis, infantile paralysis, Heine-Medin disease) is a common virus disease which usually runs a mild course characterized by upper respiratory or gastro-intestinal involvement. But there is, in severe cases, a tendency of invasion of the central nervous system leading to flaccid paralysis of voluntary muscles. Damage to the central nervous system is at times sufficient to cause death.

Basically poliomyelitis is an infection of the lining of the bowel, prone to pass more deeply into the body, in part carried by the blood stream, in part by passage along nerve paths (Burnet). Poliomyelitis can be caused by three main immunologically different types of the virus This suggests that from the etiological viewpoint, poliomyelitis is not a single disease but rather one caused by a family of viruses (Salk) Each of the three types is capable of causing paralysis in man, each, however, will immunize only against viruses of the same type but not against members of the other type. These are now referred to as types 1, 2, and 3 instead of the former designations which were the names of the prototype viruses—Brunhilde, Lansing, and Leon—which served as the basis for the establishment of the classification into three immunologic types (Salk) All three types are pathogenic for monkeys The most dangerous viruses for humans are those of type 1

According to Bodian, poliomyelitis virus multiplies first in the alimentary mucosa, then in the organs associated with the blood and finally in the central nervous system. Viremia is already initiated by the escape of virus from the alimentary multiplication sites and may be brought to an end by the appearance of antibodies.

There is evidence of widespread involvement of various peripheral areas, including lymphatic tissue, and skeletal and cardiac muscle. In other words, the entire evolutional pattern of poliomyelitis seems to imitate closely that of generalized viral infections of childhood, i e. measles and mumps, in which invasion of central nervous system is merely a comparatively rare and terminal accident (Jungeblut and Huenekens).

Cardiovascular involvement in poliomyelitis has been demonstrated by numerous authors. The earliest pathologic report of heart involvement was reported by Medin (1890), who observed cloudy swelling of the myocardium, liver, and kidneys in poliomyelitis.

Robertson and Chesley (1910) described swelling of myocardial fibers

accompanied by interstitial edema in four of six patients dying from poliomyelitis Hertz, Johnson and Depree (1922) reported on a patient who recovered from an attack of infantile paralysis with optic neuritis and myocarditis of several months' duration.

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It seems possible that poliomyelitis-carditis may be caused by direct action of the virus on the heart muscle. A direct etiological relationship between myocarditis and the virus has found its experimental verification by Jungeblut and Edwards. In poliomyelitis, tissue invasion may be preceded by viremia which is followed by invasion of the infectious agent into susceptible cells. At a later stage the virus probably disappears from the circulation since no virus could be recovered from a specimen of liver at the time of necropsy. But it was recovered from hearts with and without myocardial involvement. Hypoxia, even a reduced concentration of labile tissue oxydase in some parts of the myocardium may contribute to enhancing the severity of heart disease (Lyon)

Saphir and Wile (1942) noted myocardial changes in as many as six of seven patients dying early in the disease. Seventeen additional cases, 10 of which had shown myocardial lesions, were described by Saphir in 1948. In nine fatal cases of bulbospinal infantile paralysis reported by Peale and Lucchesi (1943) myocarditis was found. Dublin and Larson (1943) described myocarditis in 2 of 12 cases of poliomyelitis and Dolgopol and Cragan (1948) in 16 of 92 cases which is equivalent to 17.4 per cent; but in 11 out of 45 cases in which multiple sections were made of each heart which amounts to 26 6 per cent Ludden and Edwards observed myocarditis in 14 of 35 cases; Clawson (1949) in 12 of 53 fatal cases of poliomyelitis Spain, Bradess and Parsonnet (1950), found myocarditis in 12 out of 14 cases, Doehnhardt (1953) in 19 out of 46 Georg, Hilden and Vimtrup (1953) found in postmortem studies of the heart, among 13 cases with respiratory paralysis, acute myocarditis in two, indefinite myocarditis in two others, non-specific changes in seven patients and no abnormality in two

Fox, Sennett and Kuzma (1953) made histological observations in 70 cases of bulbar poliomyelitis On microscopy, an interstitial inflammatory reaction was evident in about half the cases (38). In 25 of these it was slight, while in 13 it would be assessed as moderate compared with the other forms of interstitial myocarditis Jungeblut and Edwards believe that the heart muscle is severely affected in approximately 30 per cent of fatal cases of poliomyelitis Teloh's report is based on 47 cases of poliomyelitis in which autopsies were done from 1942 to 1952 inclusive.

Acute myocarditis was observed in 26 patients (55 3 per cent). During the epidemic of 1949, the incidence of myocarditis was much greater than in any other year (100 per cent) and it was also severer This is addi-

tional evidence to that collected by other authors, that during certain epidemics there are viscerotropic strains of the virus which may injure the myocardium. The occurrence of acute myocarditis in these cases *could not* be correlated with the sex or age of the patient or with the occurrence of cardiac dilatation or hypertrophy. The occurrence seems more common and also more severe with advancing age in the cases of Weinstein and Shelokov.

Jurow and Dolgopol observed acute focal myocarditis in 32.9 per cent of 73 cases of poliomyelitis in which multiple sections of myocardium were available. The largest number of cases was seen in patients dying between the third and fifth day from the onset of the disease. This was true of the older (1948) as well as of the more recent series (1953). The occurrence of focal myocarditis was not related to the presence or absence of pneumonia.

Extensive myocarditis has also been described in the newborn (Baskin, Soule and Mills, Jungeblut and Edwards, Wright and Owen). Possible clinical criteria of myocarditis in poliomyelitis include changes in blood *pressure, sudden or disproportionate tachycardia or bradycardia (tic-tac* rhythm), changing qualities of heart sounds and murmurs, diminished intensity of the first heart sound in the mitral area, transient arrhythmia, signs of pulmonary edema, cardiac decompensation and shock (Joos and Yu). Myocardial involvement is often mild and easily overlooked. If there is cardiac insufficiency low output heart failure may develop (Schmidt-Kessen). Dyspnea, cyanosis, thready pulse and generally a turn to the worse may be suggestive of severe myocarditis (Saphir). However, respiratory distress may be the result of spinal cord or medullary involvement so that dyspnea and cyanosis are of little value in the diagnosis of myocarditis (Ludden and Edwards). The presence of myocarditis in the subclinical phase may be a factor contributing to prolonged convalescence and debility (Spain, Bradess and Parsonnet).

In part of poliomyelitis cases there is hypertension observed even in purely spinal and non-paralytic mild cases. Lachmund described hypertension occurring in 22 out of 208 patients with poliomyelitis. His patients with hypertension were chiefly severely ill with bulbar symptoms. Twelve of 92 died. Arterial hypertension associated with acute anterior poliomyelitis has been noted in over half the patients seen at New York Hospital during two years by McDowell and Plum; they found that it was not only relatively common in acute poliomyelitis but was also

It seems possible that poliomyelitis-carditis may be caused by direct action of the virus on the heart muscle. A direct etiological relationship between myocarditis and the virus has found its experimental verification by Jungeblut and Edwards. In poliomyelitis, tissue invasion may be preceded by viremia which is followed by invasion of the infectious agent into susceptible cells. At a later stage the virus probably disappears from the circulation since no virus could be recovered from a specimen of liver at the time of necropsy. But it was recovered from hearts with and without myocardial involvement. Hypoxia, even a reduced concentration of labile tissue oxydase in some parts of the myocardium may contribute to enhancing the severity of heart disease (Lyon).

Saphir and Wile (1942) noted myocardial changes in as many as six of seven patients dying early in the disease Seventeen additional cases, 10 of which had shown myocardial lesions, were described by Saphir in 1948. In nine fatal cases of bulbospinal infantile paralysis reported by Peale and Lucchesi (1943) myocarditis was found Dublin and Larson (1943) described myocarditis in 2 of 12 cases of poliomyelitis and Dolgopol and Cragan (1948) in 16 of 92 cases which is equivalent to 17.4 per cent, but in 11 out of 45 cases in which multiple sections were made of each heart which amounts to 26 6 per cent. Ludden and Edwards observed myocarditis in 14 of 35 cases, Clawson (1949) in 12 of 53 fatal cases of poliomyelitis Spain, Bradess and Parsonnet (1950), found myocarditis in 12 out of 14 cases, Doehnhardt (1953) in 19 out of 46. Georg, Hilden and Vimtrup (1953) found in postmortem studies of the heart, among 13 cases with respiratory paralysis, acute myocarditis in two, indefinite myocarditis in two others, non-specific changes in seven patients and no abnormality in two

Fox, Sennett and Kuzma (1953) made histological observations in 70 cases of bulbar poliomyelitis. On microscopy, an interstitial inflammatory reaction was evident in about half the cases (38). In 25 of these it was slight, while in 13 it would be assessed as moderate compared with the other forms of interstitial myocarditis Jungeblut and Edwards believe that the heart muscle is severely affected in approximately 30 per cent of fatal cases of poliomyelitis Teloh's report is based on 47 cases of poliomyelitis in which autopsies were done from 1942 to 1952 inclusive.

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maintaining adequate ventilation. Although all students of poliomyelitis have noted instances in which the blood pressure has been elevated for a period of time longer than could be accounted for by hypoxia alone or, for that matter, has remained high in the convalescent phase, such cases are distinctly uncommon. The mechanism for the production of persistent hypertension, not influenced by the state of oxygenation is probably quite different from the one responsible for short-lived episodes. Bulbar lesions in areas in which the pressoreceptor fibers of the vagus and glossopharyngeus nerves terminate, explain the high blood pressure which occurs in bulbopontine forms of poliomyelitis. This hypertension is also termed "infectious high pressure."

Patients who have been observed for a long period of time appear to have again a normal blood pressure, this central type of hypertension has been readjusted by the modulator influence of higher situated centers which are still active in individuals with such a hypertension (Lachmund).

McDowell and Plum emphasized that anoxemia, hypercapnia or artificial respiration appeared to intensify and prolong the otherwise transient hypertensive state. The appearance of arterial hypertension in their patients may have been the primary result of the invasion of brain-stem autonomous structures by poliomyelitis virus or may have been a manifestation of generalized bodily reaction to prolonged anxiety. Investigations of Bolt, Valentin and Venrath leave us with scant doubt that the cause of hypertension with progressive weakness and paralysis of respitatory muscles is hypercarbia and hypoxemia produced by suboxygenation. In such cases acute left ventricular failure and pulmonary edema may be prominent terminal features (Doehnhardt).

Smith, Harris and Rosenblatt emphasized that in poliomyelitis patients with arterial hypertension, the face was ashen grey not unlike that seen in acute coronary thrombosis With venous hypertension, cyanosis was prominent.

According to Hoff and Seitelberger, degeneration of the medial layers of the formatio reticularis of the medulla oblongata may lead to cardiovascular collapse and death.

The earliest electrocardiographic observations to be made were those of Peabody, Draper and Dochez (1912) who were studying the terminal arrhythmia An illustration in their paper shows pronounced sinus arrhythmia which was attributed to vagal disturbances.

Battro, Cabils-Aguirre and Mendy found electrocardiographic evidence

found in comparatively benign forms. Frequent blood pressure readings were taken on each of 95 patients and when a diastolic pressure of over 90 lasted for a period of more than 12 hours, hypertension was considered present.

Perlstein, Andelman, Rosner and Wehrle observed in 195 cases, one-third non-paralytic and two-thirds paralytic, 65 presenting evidence of hypertension at some point during their illness. Hypertension was usually very transient and lasted from two to four days, but for several months in severe respiratory cases. In this series the average diastolic rise was 29 mm. Hg; the highest 63 mm. Hg, the lowest 15 mm. Hg.

Hypertonic circulatory alterations are frequently observed when the blood pressure of patients is daily controlled. Platou considers marked fluctuation or definite elevation in blood pressure to be one of the most valuable signs in predicting the onset of bulbar involvement.

Grules and Panos noted hypertension in 51 of 70 cases, i e in 72.9 per cent of patients with bulbar poliomyelitis Elevated blood pressure was found in only seven per cent of the spinal forms and in 12 per cent of the non-paralytic forms of the disease It had been maintained that hypoxia in the absence of visible cyanosis may result in a compensatory elevation of the blood pressure However, the persistence in several instances for several days after continuous administration of oxygen by mask, intratracheally or by oxygen tent suggests that damage to the cardiovascular centers was the causative factor

McDowell and Plum found the highest incidence of hypertension in patients with bulbospinal paralysis or paralysis of all extremities. Hypertension was greater and of longer duration in patients needing artificial respiration. Twenty-nine of 30 patients requiring artificial respiration were hypertensive, among those who survived the acute phase of the disease. Average pressure was 164/104 mm Hg and the average duration was 98 days. Ten patients still had hypertension 3 to 12 months after onset of illness.

According to Smith, Harris and Rosenblatt, pulmonary angiospasm produced by vasomotor center disturbance may result in right ventricular failure, pulmonary edema and death. In the fatal cases right sided cardiac dilatation and in the more marked cases left sided cardiac dilatation was also noted.

Weinstein and Shelokov observed that hypertension is relatively common in acute poliomyelitis. Its development in most cases is probably related to hypoxia; return to the normotensive state can be produced by

complex and ST segment changes appeared transiently and were less frequent. Abnormal T waves usually occurred early, and the prolongation of QT persisted for the longest duration. The incidence of abnormality of electrocardiograms was higher in adults than in children and in patients with bulbar and high cervical paralytic lesions. Although the incidence of electrocardiographic alterations *during the course of acute poliomyelitis* was high, all the changes observed were considered to be non-specific. Whereas in the majority of patients the abnormal changes both appeared and reverted to normal within the first four weeks, a small number of patients still showed abnormalities several months after the onset of disease.

Gefter, Leaman, Lucchesi, Maher and Dworin found abnormal electrocardiograms more frequently in severe cases of poliomyelitis. The main alterations were abnormally high and peaked P waves, prolonged PR intervals, deviation of ST segments, flat diphasic or inverted T waves, left axis deviation, right axis deviation

Bradford and Anderson reported high grade sinus tachycardia ST and T changes, conduction disturbances Three of their fatal cases displayed *pathologic electrocardiograms The only fatal case with a normal electrocardiogram* did show at autopsy a slight amount of both perivascular and diffuse cellular infiltration

Frischknecht and Zellweger found pathological T waves and disturbances of the auricular conduction in their cases of acute poliomyelitis. Before the fifteenth day of the disease the pathological T waves were often spontaneously reversible and could be partly normalized by sympathicolytic agents This might point to a probability of "extracardiac vegetative disregulation" of the heart Changes of the electrocardiogram lasting longer than two to three weeks were suspected of myocarditis Only four such cases were found. Long lasting changes of the electrocardiogram are caused by direct viral action on the autonomous nervous system or on the myocardium

According to Weinstein and Shelokov a wide variety of electrocardiographic changes varying from minor T wave alterations to a pattern suggestive of myocardial infarction have been observed in poliomyelitis. There seems to be little doubt that the severity of the infection of the central nervous system is an important factor

Reubi and Bornstein were of the opinion that in their series the presence of electrocardiographic changes was directly related to the severity of

of transient myocarditis in four of 20 cases in the acute stage of the infection.

Gefter, Leaman, Lucchesi, Maher and Dwotin found abnormal electrocardiograms in 14.2 per cent of their 226 poliomyelitis cases.

Bradford and Anderson found abnormal electrocardiograms in about 12 per cent of their 155 cases. Laake observed electrocardiographic changes in 31.7 per cent; in his patients with the spinal type of poliomyelitis associated with moderate paresis, the incidence of abnormal electrocardiograms was 25.5 per cent while in patients with extensive spinal involvement it was more than 50 per cent. In bulbar poliomyelitis it was 40 per cent.

Weinstein and Shelokov observed in 1947 among 57 cases, 14 with electrocardiographic alterations, and in 1949 among 28 cases of poliomyelitis, 11 with abnormal electrocardiograms. Frischknecht and Zellweger detected in 21 cases of 52, abnormalitites demonstrable by electrocardiogram Reubi and Bornstein reported abnormal findings in 31 among among 52 poliomyelitis patients. Bengtsson and Johnsson submitted 200 cases of acute poliomyelitis to serial electrocardiography and found changes in 11 5 per cent

Mule and Angelini found, in 9 out of 40 cases of poliomyelitis, abnormal electrocardiograms which returned to normal during convalescence.

Rose took electrocardiograms in 55 children with poliomyelitis and found abnormalities in 13. The lowest incidence was in the non-paralytic group, the highest in the bulbospinal group. Doehnhardt found abnormal electrocardiograms in 43 per cent of 472 cases of poliomyelitis.

Fox, Sennett and Kuzma took electrocardiograms on admission, one week later and on discharge Among 189 cases, 61 (32 4 per cent) were found to have definite abnormalities. The wide difference between some of the figures of electrocardiographic abnormalities of various authors reflects differing criteria of abnormality [the inclusion of sinus tachycardia as an abnormality in one paper (Manning and Yu) and its absence in another (Bradford and Anderson)]

Joos and Yu observed, in electrocardiograms taken in 23 patients with acute poliomyelitis, that the QT_c was prolonged in five patients. Manning and Yu continuing these studies observed among 150 patients, 116 abnormal electrocardiograms at some time during the disease The most common findings were abnormal T waves, tachycardia and abnormal QT_c. Various arrhythmias, prolonged PR interval, a low voltage QRS

complex and ST segment changes appeared transiently and were less frequent. Abnormal T waves usually occurred early, and the prolongation of QT persisted for the longest duration The incidence of abnormality of electrocardiograms was higher in adults than in children and in patients with bulbar and high cervical paralytic lesions. Although the incidence of electrocardiographic alterations during the course of acute poliomyelitis was high, all the changes observed were considered to be non-specific. Whereas in the majority of patients the abnormal changes both appeared and reverted to normal within the first four weeks, a small number of patients still showed abnormalities several months after the onset of disease

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paralysis. Alterations most indicative of myocarditis i.e. depression of ST segments and inversion of T waves were chiefly encountered in the bulbar and severe spinal forms. It is possible that electrocardiographic alterations are also caused by neurovegetative factors.

Laake found, in his 84 cases of poliomyelitis with abnormal electrocardiograms, four with delayed auriculoventricular conduction time for one week, four showed disturbance of sinus rhythm which improved within two days in two; 15 presented pathological P waves in lead II, III and 21 showed abnormal P waves, ST intervals and T waves which were usually transitory and 40 showed transitory abnormal ST waves and/or abnormal T waves Prolongation of QT interval was observed in only one single case. The electrocardiogram became normal in 34 of the 50 patients in whom repeated records were obtained. Definite improvement of the electrocardiogram occurred in nine cases, the changes persisted in seven patients. In two of the three patients who died, histological examinations revealed interstitial myocarditis, in the third case, there was pronounced fibrous tissue formation, cellular infiltration and fragmentation of myocardial fibers Definite conclusions as to the incidence of functional or organic changes of the heart could not be drawn on the basis of these cases

Bengtsson and Johnsson found abnormal electrocardiograms in 3 of 72 children and in 20 of 128 adults. The abnormalities consisted of abnormal T waves, QT prolongation, disturbances of rhythm such as A-V block, auricular flutter and fibrillation Sympathicotonia as the cause of electrocardiographic alterations was observed in several cases These electrocardiograms were not included in the 11 5 per cent showing pathologic changes. Electrocardiographic alterations were most frequently found in cases with damage of the vago-glossopharyngeal nucleus. However, the non-paralytic cases also showed a fairly high incidence of pathologic electrocardiograms Among the clinical findings, relative tachycardia of comparatively long duration, as a subjective heart trouble was noted during convalescence The majority of electrocardiographic alterations appeared during the first or second week of the disease, persisted for three to four weeks—in some cases less and in others more—or between six months and one year.

According to Schmidt-Kessen, electrocardiographic alterations in poliomyelitis consist in prolonged PR interval, broadening of QRS complexes, P alterations prolongation of QT, inversion of T waves, especially in

chest leads (V_{3-6}), less in the limb leads. Owing to their focal distribution myocardial involvement often manifests itself in the electrocardiogram by a so-called inflammatory "T." Sympathicotonia may also influence the electrocardiographic pattern in poliomyelitis patients.

Fox, Sennett and Kuzma found in their 61 cases with abnormal electrocardiograms, ST depressions and/or T waves changes in 96 per cent. Changes in conduction whether superventricular or ventricular were unusual. QT prolongation was observed in 1.6 per cent of the cases. The electrocardiographic changes were noted as early as the first day of illness and usually developed during the first week. Lead AVF disclosed the earliest and sometimes the only abnormality. Of the nine patients with bulbar involvement three had abnormal electrocardiograms. Clinical evidence indicative of myocarditis was obtained in four cases.

Georg, Hilden and Vimtrip reported that in their 62 cases of paralytic poliomyelitis there were electrocardiographic alterations in five cases of which four were treated in the respirator and the fifth had respiratory paralysis In nine cases the electrocardiogram was borderline, six of these cases had paralysis of the respiratory muscles. The electrocardiographic changes were, in one case, nodal rhythm and increased QT; this case showed myocarditis at autopsy In all other cases the electrocardiogram showed moderate ST and T changes The authors think that the majority of the pathological and electrocardiographic changes found in poliomyelitis cases are due to anoxia and altered pulmonary circulation.

Doehnhardt in his cases found most frequently alterations of the ST segment and of T waves and QT prolongation. QT prolongation was observed in 28 of ninety cases, this Hegglin phenomenon was observed in paralytic cases with and without respiratory embarrassment. Hypoxia and hypopotassemia are not regarded as the decisive cause of the QT prolongation The finding of interstitial myocarditis—sometimes marked, diffuse cell infiltrations, focal necrosis of myocardial fibers and some nerve lesions—explains the occurrence of various electrocardiographic changes in poliomyelitis But a greater or lesser part is to be considered as non-specific and may be produced, partly by neurovegetative derangement. Electrocardiographic alterations are also caused by energetic (dynamic) cardiac insufficiency QT prolongation is a significant electrocardiographic feature in many cases of this illness. The factors which may lead to this phenomenon have not yet been sufficiently studied. Complex biochemical alterations in poliomyelitis play a role in the development

paralysis. Alterations most indicative of myocarditis i.e. depression of ST segments and inversion of T waves were chiefly encountered in the bulbar and severe spinal forms. It is possible that electrocardiographic alterations are also caused by neurovegetative factors.

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tected by serum examination Hyperpotassemia may be found with shock and respiratory acidosis, in which case therapy is primarily directed toward restoration of the pulmonary ventilation, diffusion and improvement of peripheral vascular tone while withholding oral or parenteral potassium.

Excessive sodium intake should be avoided particularly during the acute phase when it may predispose to hypotassemia and metabolic alkalosis. During the course of disease occurrence of complications such as extension of the disease process, pulmonary edema, atelectasis, respiratory acidosis, metabolic alcalosis and hemolytic reactions with hepatic involvement may be detected early by recurrence of increased nitrogen and potassium excretion

The serum albumin fraction of the blood protein drops in a manner parallel to the clinical severity of the disease, beginning between the first and third day of illness and reaching its lowest level by the tenth day The progressive drop in serum albumin levels was retarded or prevented in some cases by the administration of pooled irradiated blood plasma, but this augmentation of serum albumin values is a temporary phenomenon requiring continuous support for an as yet undetermined length of time in order to obtain sustained clinical effects

Kelly, Briggs and Jensen (1946), Kelly, Doeden, Hall and McQuarrie (1949) observed abnormalities in the beta disturbance of the electrophoretic patterns of the serum in poliomyelitis, but these investigators, however, did not report values for the protein components of the serum. Routh and Paul, who made electrophoretic studies of plasma and serum proteins in poliomyelitis, found albumin decreased while the alpha[1] and alpha[2] globulins and the fibrinogens increased over average values for normal individuals The gamma[1] globulin was found to be normal in poliomyelitis and the gamma globulin fraction was decreased in all types of poliomyelitis

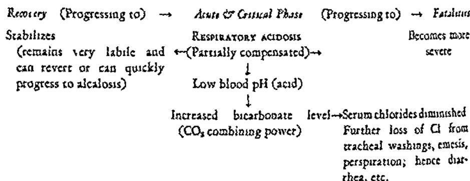
Steigman, Brodsky and Stephens reported normal frequency distributions for values of serum protein and albumin in poliomyelitis. Slight, but significant differences of serum protein were found only in the chronic stage and were explained, in part, by nitrogen deficits associated with the prolonged immobilization of convalescence

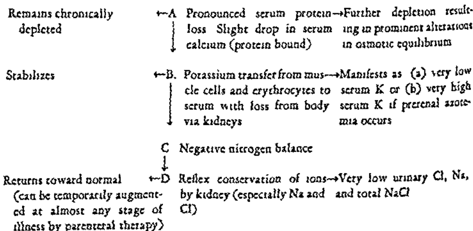
Bower and his associates reported low serum potassium values at some stage of poliomyelitis in over half of their cases Earle reported low serum potassium levels in ten patients with severe spinal or bulbar poliomye-

of impairment of the myocardium with possible consecutive electrocardiographic changes.

Bower, Chudnoff and Chaney observed important metabolic changes during the acute phase of poliomyelitis. They were alterations of serum proteins, electrolytes of the blood and of the urine, which the authors summarized diagrammatically. The principal trends of the biochemical changes, according to Bower, Chudnoff and Chaney are given here:

MAJOR ELECTROLYTIC ALTERATIONS IN ACUTE HUMAN POLIOMYELITIS





According to Bower, Chudnoff and Chaney and to Bower, Morgan and Chaney, a marked degree of negative nitrogen balance occurs in the acute phase of poliomyelitis This negative balance is accompanied by a precipitous drop in serum albumin, elevation of globulin and a negative potassium balance. Hypotassemia is frequently present and may be de-

tion may develop. It is possible that cases of myocarditis in severe poliomyelitis represent, entirely or partly, hypokalemic myocarditis.

According to Bower, Morgan and Chaney the acute catabolic phase of poliomyelitis is characterized by excretion of large quantities of nitrogen and potassium in the urine, indicative of protoplasmic breakdown. Where extensive potassium excretion is apparent extensive paralysis may occur but there may be a normal potassium level combined with a negative potassium balance. Such cases emphasize the inadequacy of calculations of cellular potassium by measurement of the extracellular ion, and this makes it understandable that little importance has been attached to potassium in poliomyelitis until now. Certain abnormal electrocardiograms in acute poliomyelitis may be consistent with potassium deficiency despite normal potassium Bower wrote that, at the later stages of poliomyelitis, when recovery and tissue regeneration are present, low serum potassium values are to be anticipated unless adequate potassium is supplied.

The development of cardiovascular concepts in poliomyelitis has led to the conclusion that the mainly cytologic approach in studying heart involvement in this illness has to be considered as incomplete. We are confronted with an intricate pattern of factors—specific (viral) as well as nonspecific (neurovegatitive, biochemical)—which influence the cardiovascular system In many cases the electrocardiogram may be helpful in establishing the diagnosis of heart involvement in poliomyelitis. There is much difficulty in unravelling the significance of single factors and their effect on the electrocardiogram. Myocarditis (viral and/or hypokalemic) should be suspected in every poliomyelitis patient who is severely ill. Cardiovascular collapse and death can be caused by myocarditis or by involvement of the *formatio reticularis medullae oblongatae*. Hypertension may be produced by hypoxemia and hypercarbia or by infectious central involvement Acute right ventricular failure caused by pulmonary complications or by pulmonary angiospasm and sudden left ventricular failure produced by hypoxia may be dangerous to the poliomyelitis patient. Pulmonary angiospasm may lead to cyanosis, pulmonary edema and death due to acute dilatation of the heart.

Energetic (dynamic) cardiac insufficiency and autonomous imbalance have also to be considered in poliomyelitis cases.

Good nursing is decisive in the treatment of patients with poliomyelitis. Respiratory paralysis is the greatest threat to life in this illness.

litis. This finding was observed in patients who had no vomiting or diarrhea and the potassium deficit was considered presumably to be the result of low intake.

Hall and Sherman underlined the importance of potassium depletion in one case of severe poliomyelitis and suggested that the myocardial and electrocardiographic changes observed in poliomyelitis might have a metabolic component. The use of serial electrocardiograms proved valuable in the detection and management of potassium deficiency and is recommended when the clinical course suggests a metabolic disturbance in this disease. In their opinion the observed episodes of gastrointestinal atony and dilatation, nausea and vomiting were due to potassium deficiency and contributed significantly to continued potassium loss, thereby establishing a self-perpetuating circle Potassium depletion of large magnitude is inherent in this circle, hence therapy must be directed toward replenishing the total body stores, not at temporarily restoring the serum potassium level or reversing electrocardiographic changes Potassium deficiency must be considered in the management of any patient severely ill with poliomyelitis

Lans, Stein, Becker, Hoyne and Meyer found, in patients with bulbar poliomyelitis, frequent association with a potassium deficiency. This deficiency is brought about by inability to swallow, vomiting and the use of parenteral infusions containing little or no potassium. An ascending Landry-type of paralysis *may* occur Patients with bulbar poliomyelitis cannot tolerate the superimposed hypopotassemia. Administration of potassium chloride resulted in a marked improvement of the condition in six patients. Doehnhardt found severe hypopotassemia in the late stage of seven poliomyelitic paralyses.

Pietrogrande, Versino-Gedo and Perticucci observed low serum potassium in old cases of severe poliomyelitis who were bedridden and immobilized in a cast.

The clinical diagnosis of hypopotassemia in poliomyelitis is difficult without proper laboratory methods because clinical symptoms of poliomyelitis and low serum potassium are identical or very similar In brief, muscular weakness and paralysis as well as various disturbances appear when the potassium metabolism is disturbed. The electrocardiographic changes in hypopotassemia are of great importance for the diagnosis. In cases with profound hypopotassemia, focal areas of necrosis of cardiac and skeletal muscles with interstitial edema and/or lymphocytic infiltra-

sary to correct potassium loss in mild and moderate cases of poliomyelitis. Adequacy of protein nutrition must be restored immediately, and orange juice, cereals and meat juice can supply potassium together with oral potassium chloride or potassium citricum. Excessive sodium intake should be avoided during the acute phase of the disease. Careful management of fluid in patients with bulbar disease is essential.

Dietotherapy in poliomyelitis may make more progress through controlled observation in carefully conducted clinical studies. Boines commends the use of hyperproteinization for minimizing the ravage of poliomyelitis and for accelerating rehabilitation. Reubi and Bornstein recommended systemic electrocardiographic examination throughout the period of convalescence before physiotherapy is started. But Schmidt-Kessen is of the opinion that an abnormal electrocardiogram is generally no contraindication for the timely institution of physical therapy.

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The indication for placing a patient in the respirator is a diminution of the vital capacity; the most practical method of recognizing diminished vital capacity is through the rise of the counting test of Smith. Frequent checks on CO_2, hematocrit and blood chemistry should be made.

The effect of serum protein alterations and hypopotassemia (or hyperpotassemia in renal shut down) should receive greater attention, especially in severe cases of poliomyelitis. Early diagnosis and proper localization of cardiovascular involvement may facilitate the treatment especially of the bulbar cases.

The diversity of cardiovascular disturbances in poliomyelitis render various therapeutic recommendations understandable.

Schmidt-Kessen recommended digitalization in all severe cases as long as there was no turn to the better.

Aschenbrenner and Doehnhardt have suggested in severe cases of poliomyelitis, the administration of cardiac glycosides, strophantin has been given in every case of poliomyelitis especially in cases associated with pulmonary complications and during respirator treatment. Prophylactic treatment with strophantin is indicated in order to avoid cardiac failure.

Smith, Harris and Rosenblatt who emphasized the importance of pulmonary angiospasm in poliomyelitis stressed the fact that tracheotomy is of value only when there is bronchial obstruction, this is generally not present in bulbar poliomyelitis. The uses of vasodilative drugs, notably Priscoline has been recommended in the treatment of vasospastic phenomena.

According to Glanzmann, the earliest treatment with large, possibly repeated blood transfusions in the preparalytic stages of poliomyelitis is promising Administration of potassium and/or repeated plasma infusions may be life-saving in severely ill patients (Bower) But in mild cases plasma infusions are not necessary

In poliomyelitic children, Dieckhoff administered 150–300 cc. (i.e 10–15 cc. per Kg of body weight) Periston N (polyvinylpyrrolidone) intravenously. Under this treatment, severe paralysis was observed to disappear In children who had been treated with Periston N during the preparalytic stage of poliomyelitis, no paralysis occurred and meningeal symptoms quickly subsided

Bower and his associates recommended that intravenous fluids should supply both fluid and hydration during the acute phase and it should contain some potassium provided the urine output is normal. It is neces-

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3. Rabies

Rabies (hydrophobia, lyssa) is an acute, often fatal encephalomyelitis caused by the bite of certain animals and is characterized by a long incubation period, hydrophobia, muscular spasms and paralysis. The causative agent is a virus The disease occurs naturally among dogs, wolves, foxes, jackals, cats, cattle, swine, horses, sheep, goats, meercats and blood sucking vampire bats. The virus is present in the saliva of infected animals. Man acquires the infection by being bitten by rabid animals. The infection may be transmitted by a rabid animal licking an abraded surface. In the absence of antirabies treatment, the chance of contracting rabies after the bite by a proven rabid dog is about 5 to 15 per cent, but once symptoms and signs of rabies develop the outcome is fatal (Rhodes and van Rooyen)

The rabies virus is a very labile agent, it loses its virulence quickly when exposed to light, heat and drying Rabies has been so exhaustively and thoroughly studied that there is scarcely anything to add to the clinical knowledge at our disposal. But the divergency of opinion regarding the spread of the infection through the body is considerable.

According to L T Webster "the movement of rabies virus in the body and from host to host is cyclic . . . Rabies virus is present in the saliva of the rabid animal When the animal bites, the saliva is introduced through the break in the skin directly into contact with the tissues, blood, lymph vessels and nerves of the new host. From this portal of entry the virus progresses in some unknown manner, probably in association with the regional nerves, to the origin of these nerves in the spinal cord or brain There it first becomes demonstrable, increases in quantity, and spreads rapidly throughout the entire brain and cord. Meanwhile, other tissues, organs and fluids have, with insignificant exceptions, remained free of virus Next, it overflows or escapes from the brain or cord along the nerves, including those to the salivary glands From the salivary glands the virus enters the saliva and passes to the mouth. Only after all this has occurred does the infected animal become sick. . . . These phenomena are remarkably regular. The virus, once in the tissues becomes

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infection has passed to the cord. The *only* distinctive feature of rabies is the presence of Negri bodies in the cytoplasma of ganglion cells, principally in the hippocampus major and the cells of Purkinje in the cerebellum, but also in the medulla and elsewhere.

The period of incubation is ten days to several months, depending on a number of factors, especially on the severity of lacerations.

In the prodromal stage there is slight fever, headache, malaise, nausea. But a sudden onset of the initial stage also occurs. In this stage there is discomfort at the site of the bite or infection and psychic alterations. The pulse may be rapid. In the following stage of *excitement there is fever, irritability, hydrophobia, muscular spasms (especially of the muscles of deglutition and respiration)* dyspnea, rapid pulse. In the last stage, there is muscular paralysis, the temperature falls, the pulse may be rapid or slow. Cyanosis, unconsciousness precede death from heart failure, asphyxia and exhaustion

Neuroparalytic accidents may sometimes develop after antirabies treatment These occurrences are attributable to sensitization produced by brain or cord material in the antirabies vaccine. A history of allergy can be obtained from many patients who develop reactions to this vaccine. A case of long lasting allergic myocarditis has been described by Lyon in a patient with a history of allergy to foreign protein. Meningitis and myelitis following administration of rabies vaccine may also last for half a year (Fodor)

Allergic manifestations of the central nervous system and the heart after antirabies vaccination can be favorably altered by the use of antihistamin drugs Antirabies inoculations are not without danger.

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established and sets up the same series of events in all mammals thus far tested."

The view that the rabies virus, after being deposited in the infected wound, *invades traumatized nerve fibers and travels along the perineuronal lymphatics or along the axis cylinders to the central nervous system*, is largely based on experiments. *According to van Rooyen and Rhodes* the role of blood and lymph requires new investigation. Experimental work suggests that the infection is spread either by the blood and lymph stream or by the cerebrospinal fluid (J Koch, Field)

While rabies virus has been but rarely demonstrated in the blood the fact that it may pass from an infected mother to the fetus indicates that infection by the blood stream is possible even though no virus may be demonstrable therein by the methods commonly in use (Field). The cerebrospinal fluid is generally held to be not infectious, though there have been some reports to the contrary. According to Field, it is possible that here the ordinary methods for demonstration of the virus are not adequate for the absence of virus from the cerebrospinal fluid

Several workers have suggested on the basis of detailed *histological examination of the nervous system that the cerebrospinal fluid is the medium by which virus invasion actually takes place. Field did not believe in the axonal transmission of rabies virus from experimentally* inoculated masseter muscles to the pons. Inoculation of the masseter muscle of rabbit with fixed rabies virus does not lead to an early paralysis of the masticatory muscles of the same side In 5 of 13 animals paralysis began on the hind limbs Severe lesions occurred in the dorsal root ganglia of both sides and were much less intense in the lumbar than in cervical region. No lesion was found in the corresponding motor nucleus of the fifth nerve even when there already was evidence of widespread involvement of the nervous system Field's experiments suggest that *infection is disseminated either by blood stream or by the cerebrospinal fluid The answer to this question must await further research*

Boyd compared the microscopic features of rabies with the findings in *poliomyelitis* and emphasizes that the picture of rabies closely resembles that of acute poliomyelitis Inflammatory and degenerative changes are found principally in the medulla, then in the cord and last in the cerebral cortex. There are the usual perivascular collars of lymphocytes The nerve cells show all stages of degeneration from chromatolysis to destruction The disintegrating cells may be surrounded by neuronophages Degenerative and inflammatory changes are found in the nerves along *which the*

caused in suckling mice by the infection with Coxsackie A virus, type A-10.

The creatine and potassium metabolism is altered in these diseased mice. Gaedeke reported tubular and absorption nephrosis in suckling mice infected with various group A Coxsackie viruses. The changes in capillar permeability and fluid retention result in oliguria and failure of adequate secretion. The renal lesion is due to widespread destruction of striated musculature

The A and B groups of Coxsackie viruses often differ from one another in other respects although some strains have properties characteristic of either group (Tobin). Serologically, the viruses are heterogenous. There are many types in group A, and fewer in group B, and others belonging to neither group.

The chief clinical picture produced by members of group A is herpangina, by group B, epidemic pleurodynia or Bornholm disease. Some outbreaks are characterized by a high incidence of dry pleuritis plus meningeal involvement. In others, the predominant symptoms are only myalgia in which muscle biopsy revealed lesions identical with those observed in infected mice. But certain clinical pictures of illness do not always show the features characteristic of a certain group of Coxsackie viruses. Epidemics of "meningoencephalitis myalgica," a form of Bornholm disease, are also caused by group A viruses. In other cases, Coxsackie viruses of group A have produced severe dermatomyositis Severest involvement of muscles in humans may be caused by group A viruses.

The diagnosis of a Coxsackie virus infection depends on virus isolation and the demonstration of a rise of antibody of the patient against the infecting strain. Isolation of the virus in suspected cases indicates that the disease occurring at the same time is due to Coxsackie virus infection. Serologic diagnosis alone is not a practical routine proposition owing to the multiplicity of virus types (Tobin).

The importance of the Coxsackie virus infection lies not so much in itself as in its potential mimicry of other severer illnesses (Hopkins). The diphasic febrile course of the infection with muscular pains and *weakness* may simulate poliomyelitis Epidemic pleurodynia may be confused with coronary insufficiency, with recurrent myocardial infarction (Huebner, Beeman, Cole, Beigelman and Bell), (Huebner, Risser, Bell, Beeman, Beigelman and Strong). The differential diagnosis is easier in patients who have normal electrocardiograms during Coxsackie virus infection.

Coxsackie viruses in humans do not usually produce cardiac involve-

CHAPTER VIII

Diseases of the Muscular System

Coxsackie Virus Diseases—Herpangina, Epidemic Pleurodynia

The first member of the group of Coxsackie viruses was isolated in 1947 by Dalldorf and Sickles. Coxsackie viruses are found in the feces, throat swabs or both, from normal people and of patients suffering from various clinical syndromes. Occasionally that virus is isolated from the cerebrospinal fluid. The Coxsackie viruses are pathogen for suckling mice, suckling hamsters, and merinos Chimpanzees and young cynomolgus monkeys can be infected subclinically Some strains have grown in tissue cultures and in fertile eggs.

After infection, Coxsackie viruses may be excreted by patients for as long as two to three months, but usually it disappears from the feces in from one to four weeks (Tobin) During epidemics, the Coxsackie viruses are widely spread. Affected persons may have the virus in the feces without showing a manifest clinical disease. Persons suffering from another disease may harbor Coxsackie viruses. Man is its chief reservoir and carrier.

The Coxsackie viruses do not comprise a homogenous group, but are separated into a number of different agents having, as a common property, a high infectivity for newborn mice Although they can induce the formation of antibodies in mice for all ages, only a few are able to produce noticeable symptoms or death in any but suckling mice.

The viruses are divided, broadly, in two groups (A and B). On biological grounds, those of group A are characterized by their ability chiefly to produce myopathia in mice The mice show a flaccid paralysis. Strains of group B may not involve skeletal muscle but affect the myocardium, liver, fat, central nervous system or may cause focal lesions in muscles and especially necrosis in the central nervous system and in viscera Strain B viruses may produce spastic paralysis

Affected muscles lose their cross striation and show hyaline degeneration with cellular infiltration.

Melnick and Godman, who described muscle necrosis followed by inflammatory lesions as a result of inoculation of the Conn 5 strain of Coxsackie virus, found myocardial necrosis in mice but to a lesser degree. Collier, Winkel and Cafiluddi reported degeneration of the cardiac muscle

CHAPTER IX

Fevers of Viral Origin Spread by Arthropods

A GROUP of fevers of viral origin spread by arthropods consists of yellow fever, dengue, and sandfly fever They are characterized by a cycle of infection involving blood sucking vectors and *susceptible* vertebrates. In dengue, sandfly fever, and urban yellow fever, the only vertebrate involved is man

The extrinsic incubation period in yellow fever is twelve days, in dengue eleven to twelve days, and in sandfly fever six to eight days before the insects become capable of infecting man It is probable that the transmission of the causal virus is not a simple mechanical process, and at least some multiplication of the virus must already occur in the vector. The period of generalization of these three diseases is short and lasts three days or a little longer, and infection of blood sucking vectors from human patients occurs in this short-lasting viremic period.

1 YELLOW FEVER

Yellow fever is an acute infectious disease characterized by fever, jaundice, albuminuria, hematemesis, and hemorrhages. According to Dick, it has long been recognized that there are great variations in the severity of the infection. Laboratory investigations have established that the classical disease associated with jaundice, hemorrhage, and black vomit, is no more typical of infection with yellow fever virus than is paralysis of poliomyelitis and that the great bulk of infections are subclinical (which may be diagnosed only by the recovery of virus or by the demonstration of antibodies) or of mild nature The mild cases which are probably the most common type of clinical infection are unlikely to be diagnosed except during an epidemic or during a search for a case in an endemic area. They are associated with pyrexia and symptoms of fever and headache lasting for two or three days The clinical diagnosis in these cases may be suggested by albuminuria and by bradycardia in convalescence (Dick).

The virus of yellow fever is present in the human blood during the latter days of the incubation period and for the first three or four days of fever But, according to Theiler, virus can be still demonstrated in a

ment. Some of our patients examined by several electrocardiograms occasionally showed minor electrocardiographic abnormalities. We also have on record the appearance of a posterolateral myocardial infarction and a Coxsackie virus infection occurring at the same time in a man, 39 years of age. Koeppe and Rhode observed the simultaneous occurrence of coronary insufficiency, thrombophlebitis, and Coxsackie virus infection (herpangina).

Heckscher (1933) described one case of pericarditis in Bornholm disease, and Bing (1933) reported an epidemic of acute pericarditis in Copenhagen consisting of six patients admitted to a single hospital ward within several weeks with the diagnosis of Bornholm disease.

Aagard and Jensen, Bower, Gerrard and McGregor, Windorfer suggest that acute pericarditis may sometimes be a manifestation or complication of Coxsackie virus infection of the Bornholm disease type.

Betke drew attention to the occurrence of an hemolytic anemia in connection with Coxsackie A virus infection. The patient was a boy, one year old. Betke stressed the fact that Coxsackie viruses may be found in the blood of patients during some weeks and still longer in the stools. Those viruses may be connected with the development of acute hemolytic anemia.

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fluid may have increased pressure, a cellular hyperalbuminosis. Delirium, convulsions, coma may precede death which is the result of hepatic, renal, and circulatory failure. Even in very severe cases improvement may sometimes occur, and recovery is possible and complete.

Macroscopic findings in yellow fever are icterus, hemorrhages in various organs of fatal cases. The liver shows extensive cloudy and fatty degenerative changes and a distinctive spotty occurrence of necrotic areas in the midzonal liver lobules Eosinophilic intranuclear inclusion bodies are found in the liver cells and are also encountered in the brain in rather large numbers. Kidney lesions may also occur. In the liver, despite the severity of the parenchymal lesion, there is a striking lack of inflammation. No fibroblasts appear, irrespective of the amount of epithelial necrosis and there is no response to the necrosis, but a widespread tendency to hemorrhage in the liver is present Because there is no proliferation of stroma nor any inflammatory change of liver, the yellow fever hepatic damage does not show postnecrotic, cirrhotic alterations of the liver, frequently occurring in the reparative activities of a damaged liver.

According to Bugher, the heart is flabby with a variable amount of subserous petechial hemorrhages and a moderate dilatation of the right ventricle The myocardium is cloudy, icteric, and soft. There is some dilatation of all the valve rings. Subendocardial hemorrhage may be present. Fatty alterations of myocardial fibres tend to be most severe beneath the endocardium and are uneven in distribution. The nuclei of muscles fibres often show hydropic changes leading to necrosis with karyolysis and vacuolization of the cytoplasma. Cannell emphasizes that the damage to the heart is not purely transitory nor is it limited to the acute phase Apart from the cloudy swelling and fatty degeneration of the myocardium there are also some secondary interstitial changes. But there is, according to Bugher, a striking lack of cellular infiltration and fibroblastic-proliferation in the heart

Cardiac symptoms are occasionally so outspoken that reference has been made to a cardial form of yellow fever. Dilatation of the heart occurs sometimes, and the effect of the virus is demonstrated by the fall in blood pressure, the lessening in the force of the apical pulsations, and the disappearance or lessening of the heart sounds as well as the electrocardiographic changes (Craig) But, according to Cannell, the lesions occurring in the heart during the course of yellow fever when considered as a whole are not sufficient to warrant a diagnosis of yellow fever being made in

monkey after intradermal inoculation of yellow fever virus in lymph nodes, spleen and bone marrow, several days after the blood becomes virus free.

Isolation of the virus can be carried out as long as it is present in the blood. Patients are infectious to mosquitoes for these first days of illness. The mosquito is not capable of transmitting infection by bite for twelve days, but remains then infectious by bite for the rest of its life.

In the urban type of the disease, the virus is conveyed from man to man by the mosquito *Aedes aegypti*. In jungle or sylvan yellow fever which occurs in parts of South America and Africa, the virus is identical with that causing urban outbreaks, but its life circle involves wild animals and forest mosquitoes. Man is an incidental host for the virus. Recovery leaves an immunity for life. The strains of attenuated yellow fever virus are in use for vaccination. Anti-mosquito measures remain important.

Attacks of yellow fever are clinically classified as extremely mild, mild, moderate, and severe. The mild cases show many characteristic signs and symptoms of the severely ill patients. The clinical course of the illness is divided in three stages. After an incubation period of three to seven days, the onset is sudden with malaise, chill, and fever. The initial (fever) period or the stage of active congestion lasts one to four days presenting severe backache and epigastric pain. The face is flushed, the conjunctiva congested, the skin hot and dry, the pulse is, at onset, strong and full reaching ninety to one hundred beats per minute, and then falls for a few days more rapidly than would be in proportion to the temperature (Faget's sign). The blood pressure is normal Temperature is high and continuous. The urine diminishes and contains albumin. Vomiting may occur.

The following period, the stage of calm or remission, lasts two to three days. Jaundice may appear, the temperature drops, the pulse falls progressively and may go below fifty, the blood pressure may decrease. The general condition may improve and recovery may result But unfavorable cases enter the period of reaction or the stage of venous stasis. The temperature is high and the pulse rate may be low The tendency to hemorrhage is marked Black vomiting may develop It may be associated with jaundice, melena, oliguria, albuminuria. The urine deposit contains granular casts, blood cells, hemoglobin, bile Terminal tachycardia, arrhythmia and muffled and anomalous heart sounds are demonstrable. The blood shows high values for hemoglobin and erythrocytes. The spinal

on the basis of studies of Wakeman and Morrell obtained in experimentally infected Rhesus monkeys In a number of those animals, all with yellow fever, they found diminished serum protein with reduced albumin/globulin ratios, terminally. The non-protein nitrogen, amino acid, urea, and rest nitrogen in the blood were considerably increased during the last hours of life. Amino acid increased both in absolute amounts and in proportion to the non-protein nitrogen Few cases were found in which there was an absolute decrease in blood-urea nitrogen. These changes were found to be terminal events No significant alterations occurred during the early stages of the disease or in those monkeys which recovered. No definite evidence of serious impairment of the kidney function was observed, except a terminal anuria probably due to an extreme reduction of blood pressure.

Lins reported on hyperpotassemia in cases of yellow fever.

Hemodynamic deficiencies and alteration of serum protein, especially the reduction of the albumin fraction, may lead more or less quickly to hypovolemia in human cases. Most deaths occur between the fifth and the ninth day of illness After the tenth day, deaths from uncomplicated yellow fever are rare Most late deaths are probably attributable to overstraining of a damaged myocardium (Kerr) Myocardial failure after *apparently full recovery is a definite hazard* Kirk reported several cases of death from myocardial failure in patients who left the hospital early in convalescence against his advice.

The use of glucose, saline, whole blood, plasma, Periston, or other plasma expanders afford a hope of recovery in cases presenting severe hepatic destruction and subsequent hypovolemia

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their presence alone. From the results of his investigations into the state of the heart, Cannell is unable to find any reason to account for the existence of a slow pulse rate which is sometimes manifest in this disease.

According to Craig, aside from the effect upon the heart, as shown by the marked bradycardia, the yellow fever virus apparently has a marked effect upon the integrity of the capillaries. During the early stage of the disease there is intensive capillary congestion, and hemorrhages occur during this time but are more severe in the later stage of the infection after the secondary rise in temperature. During the first three days there may be epistaxis; the gums, and later the mucous membranes, bleed easily.

Chagas and Freitas, and Lins made electrocardiographic studies in yellow fever. They found a variety of changes in their tracings indicative of the many possible lesions of the myocardium. Chagas and Freitas concluded that marked and progressive changes in the T waves were of very grave prognostic import Berry and Kitchen found that these changes were not incompatible with survival in their patients Electrocardiographic studies show definitely that the heart may be involved in the very onset of the illness, and that in some mild cases the heart may be the chief seat of abnormality while in others it may escape entirely. According to Lloyd, heart lesions may also occur in the sinoauricular and the bundle of His; in these sites the changes are in accordance with the clinically observed bradycardia and alterations in the electrocardiogram. According to Bugher, the involvement of the conduction system in yellow fever is of considerable clinical importance Bradycardia during convalescence is a common finding and is frequently associated with other evidence of myocardial insufficiency Sudden death following exertion during convalescence has often been observed and occurs probably upon the basis of myocardial damage. Craig writes that, in rare instances, the damage in the heart is so great that a chronic myocarditis develops and causes the death of the patient.

Information is yet too meager to warrant a definite opinion upon the metabolic changes in yellow fever Lins found the total non-protein nitrogen of the blood markedly increased in six patients, five of whom died. Urea nitrogen was increased in three patients, but creatinine was normal. Lins found amino-acid nitrogen much increased, especially in severe infections

There is some knowledge of the way physiologic processes are disturbed

on the basis of studies of Wakeman and Morrell obtained in experimentally infected Rhesus monkeys. In a number of those animals, all with yellow fever, they found diminished serum protein with reduced albumin/globulin ratios, terminally. The non-protein nitrogen, amino acid, urea, and rest nitrogen in the blood were considerably increased during the last hours of life. Amino acid increased both in absolute amounts and in proportion to the non-protein nitrogen Few cases were found in which there was an absolute decrease in blood-urea nitrogen These changes were found to be terminal events. No significant alterations occurred during the early stages of the disease or in those monkeys which recovered. No definite evidence of serious impairment of the kidney function was observed, except a terminal anuria probably due to an extreme reduction of blood pressure

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2. Dengue Fever

Dengue fever is an acute infectious, often epidemically occurring, disease which is characterized by fever of short duration with severe headache, pains in the back and the limbs ("breakbone fever"), a rash starting in the hands spreading rapidly over the body which fades within two to three days.

The causative agent is a virus; *Aedes aegypti* and other mosquitoes are its vectors. The patient's blood is infective for mosquitoes in the incubation period and the first days of the illness. Recurrent infections with dengue are not rare. Immunity is only transient, but repeated infection produces final immunity.

The prognosis of dengue is good, the mortality is exceedingly low. Little is known regarding the pathologic picture in fatal cases. Degenerative changes in the liver, kidneys, heart and brain, and multiple, small capillary hemorrhages in the endocardium, pericardium, myocardium, pleura, peritoneum, mucosa of the stomach and of the intestines have been observed. Pulmonary edema also occurred. A serous effusion in the pericardial sac was occasionally seen The chief abnormality of dengue fever develops in and about small blood vessels and consists of endothelial swelling, perivascular edema, and a mononuclear infiltration (Goldsmid, Photakis, Mellissinos). There are three stages of the clinical course of dengue fever, the invasion, the remission, and the terminal fever. After an incubation period of four to fourteen days there is sudden onset with fever, violent headache, localized between the eyes, pain in the back and limbs The first fever period lasts for one or two days. A slight primary rash is sometimes observed during these first days of the disease and affects the face, the chest, the neck, the arms, the knees, or elbows It may either disappear or merge into the secondary rash which develops later in the disease.

There is a decrease of temperature for one or two days, on the fifth day a second attack of a two days' terminal fever follows, and a morbilliform or scarlatiniform rash develops for some days with following slight

desquamation. The blood shows leucopenia which may persist into the convalescence

At first there is tachycardia followed later by bradycardia and hypotension.

It is during convalescence that a marked slowing of the pulse sometimes occurs, at which time it is usually decreased in tension and may be more or less irregular, following severe infection (Craig).

In severe cases, hemorrhage may occur from the stomach, nose, genitourinary tract, kidneys, and bladder. Subcutaneous skin hemorrhages appear. Encephalitis may also occur. Postdengue debility is present. Wakil and Hilmy reported death from cardiac complications in the Cairo outbreak of 1937. Peripheral circulatory collapse, particularly in cardiac patients, was mentioned by Seneca.

The syndrome of neurocirculatory asthenia is a rather frequent sequel to dengue (Sydenstricker).

We also observed pain and discomfort in the precordium but normal electrocardiograms in 12 cases.

Recovery is spontaneous The patient should be kept in bed until the rash has disappeared, the blood pressure is normal, and the debility has gone.

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3 Sandfly Fever

Sandfly fever (pappataci fever, phebotomus fever) is a widely distributed specific fever of short duration caused by a virus and introduced by the bite of the female sandfly, *Phlebotomus pappataci* The incubation period is from four to seven days The onset is sudden with a chill, headache, and generalized pain. Nervous symptoms may occasionally simulate lymphocytic choriomeningitis The temperature is elevated for three days when it begins to fall The pulse is slow. Vomiting is an initial

symptom in a quarter of cases. There *may* be early constipation, late diarrhea. There is no rash. The slow pulse may persist during convalescence. Fatalities in sandfly fever are unknown. Residents in endemic areas of sandfly fever become finally resistant after repeated exposure.

It has been suggested that there is an increased capillary permeability in sandfly fever. There may be epistaxis and, occasionally, hemorrhages from the stomach, attacks of diarrhea with hemorrhage from the bowel, and neuroretinitis, papilledema, and alterations of retinal vessels. Treatment consists of rest in bed from five to six days, light diet, and some symptomatic therapy.

REFERENCE

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CHAPTER X

Diseases of Uncertain but Possibly Viral Etiology

1. Hamman-Rich Syndrome

Since Hamman and Rich reported on four patients whose lungs, on autopsy, revealed diffuse interstitial fibrosis, extensive and brief reports of this pulmonary disease have appeared presenting clinical and pathologic particulars of different phases of the disease. The disease is termed "acute diffuse interstitial fibrosis," "diffuse fibrosing interstitial pneumonitis," "cirrhosis of the lung," and "idiopathic pulmonary fibrosis." The cases may be referred to as the Hamman-Rich syndrome, a term which signifies "a syndrome rather than a disease because of some uncertainty as to the common origin of these cases" (Peabody Jr., Buechner, and Anderson).

The acute stage of the disease is characterized by a sudden onset, cough, dyspnea, cyanosis, and occasional hemoptysis in association with few pulmonary findings and an afebrile course The course is downhill with long duration and a tendency to cor pulmonale and erythrocytosis. Deaths result from either respiratory failure or cardiac decompensation. Cases of the disease may represent a fulminating form, an intermediate type, and also a chronic variety The disease—after onset of pulmonary symptoms—has been described as lasting from four weeks to many years.

The diagnosis has also been made from the study of autopsy material or from a biopsy specimen taken at the time of exploratory thoracotomy or by direct biopsy during the course of the disease and later confirmed by postmortem studies

The genetic implications of the occurrence of the Hamman-Rich syndrome in identical twins and in two brothers are interesting. The disease is unusual, but it is probable that the Hamman-Rich syndrome is not such a rarity as the paucity of former pathological reports seems to indicate The list of reported authentic cases now numbers more than thirty. Many potential cases are mentioned, but the descriptions are too scanty to verify their exact identity

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of T waves. Almost one-half of the patients show some degree of cor pulmonale; other patients have blueness of fingernails, enlargement of the ends of fingers, toes, and occasionally, erythrocytosis. X-ray examination does not provide much information regarding the presence of cor pulmonale. Many cases finally pass into a combination of congestive heart failure and terminal pneumonia. Because of the borderline pulmonary reserve of these patients, a slight respiratory infection is often fatal.

Laboratory studies are, on the whole, inconclusive; occasionally the serum albumin is reduced; a hyperglobulinemia may also occur.

Symptoms of cough, dyspnea, cyanosis, and hemoptysis associated with the mentioned roentgen findings are normally not sufficient to establish a clinical diagnosis with certainty during lifetime. The diagnosis can only be established by a study of pulmonary tissue obtained by lung biopsy or at autopsy. The most distinctive feature is the microscopic appearance of the Hamman-Rich syndrome.

Histologic investigations revealed:

(1) A type of inflammation that differed from that of ordinary pneumonia produced by pyogenic bacteria
(2) Enlargement of the lining of the alveolar epithelial cells.
(3) Necrosis of alveolar and bronchiolar epithelium.
(4) Formation of hyaline membranes which lined the alveoli, but this was not observed in all cases
(5) More or less marked edema and fibrin deposit in the alveoli walls.
(6) Profuse, diffuse, and progressive interstitial proliferation of fibrous tissue throughout all lobes of both lungs associated with focal organization of intra-alveolar hemorrhages. Eosinophil cells may be present in the interstitial tissues or may be absent.
(7) Stainable bacteria were usually not demonstrable in the lesions.

All authors underline the fact that the essential and remarkable feature of the condition is the extensive proliferation of connective tissue within the alveolar walls

Peabody Jr., Buechner and Anderson emphasized the progression of their cases from an initial stage of vigorous fibroblastic proliferation and round cell infiltration to one of extreme fibrosis.

According to Golden and Bronk, the condition is characterized by diffuse alveolar wall hypertrophy on the basis of marked capillar proliferation This angiosis is limited to the alveolar walls and accounts for their

The reported cases did not show a predominance of the disease in any racial, sex, or age group. Ages ranged from 21 to 72. The occupation of the patients is not important and does not comply with any specific toxic agent.

In one-third of the cases of Hamman-Rich syndrome, there was a prodromal period of months or years, associated with symptoms of cough, weakness, and weight loss before an acute, sometimes fulminating, progress of the disease set in, in other cases, the decline was "almost imperceptible and extended over many years." The histories of the patients usually failed to indicate pulmonary diseases which may have led to pulmonary fibrosis or a preceding viral, influenzal, or atypical pneumonia, but in the history of a few cases repeated attacks of pneumonia were mentioned. Some clinical studies during the prodromal period did not disclose clinical or roentgen evidence of pre-existing pulmonary disease. No bacterial agent could be incriminated as a possible etiologic factor. Sputum smears and cultures were negative for acid-fast bacilli and for fungi, although occasionally some bacteria could be recovered from one or another of the specimens. But the sputum did not usually contain the purulent material indicating suppurative inflammation. Many patients—almost all on antibiotic therapy—were afebrile during the more or less long duration of the disease Leucocytosis occurred sporadically throughout the disease but was not persistent. In many cases, the acute phase was ushered in by an abrupt onset of cough, fever, dyspnea, and cyanosis. During the acute phase there was increasing dyspnea, cyanosis, and sometimes hemoptysis, but in chronic cases these points were reached after years. Roentgenograms of the chest conform to no set pattern; they show, occasionally, parenchymal and hilar densities, occasionally an increase in density may be demonstrable The densities may start in the lower pulmonary lobes and may extend to involve the entire lung. Chest films sometimes revealed vascular congestion, pulmonary fibrosis, and emphysema. Clinical findings were. limited excursions of the lung, slight dullness of the chest, hyperresonance to percussion; breath sounds were often diminished, there were fine and coarse rales in both pulmonary bases. The heart was more or less enlarged to percussion Sometimes systolic murmurs were heard, the pulse and blood pressure were variable In some patients, there was roentgenologically demonstrable dilatation of the heart, prominence of the pulmonary artery segment of the heart. The electrocardiogram is frequently a dextrogram with some inversions

of T waves. Almost one-half of the patients show some degree of cor pulmonale; other patients have blueness of fingernails, enlargement of the ends of fingers, toes, and occasionally, erythrocytosis. X-ray examination does not provide much information regarding the presence of cor pulmonale. Many cases finally pass into a combination of congestive heart failure and terminal pneumonia. Because of the borderline pulmonary reserve of these patients, a slight respiratory infection is often fatal.

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Hamman and Rich assume that either a virus or a chemical irritant is responsible for the disease. Spain believes that diffuse interstitial pulmonary fibrosis produces a *distinct* clinicopathological syndrome and is caused by virus infection. According to Rubin, Kahn, and Pecker, the disease is produced by a virus, and the particular pathological features represent a type of a tissue response *which may* be associated with more widespread involvement. Katz and Auerbach believe that the non-specific diffuse pulmonary fibrosis represents the end stage of a previously existing active process of *which an allergic reaction* may have been a part. Callahan, Sutherland, Fulton, and Kline maintain that the pathogenesis of the condition does not appear to be the basis of a previous or concomitant bacterial infection The lack of cellular infiltration in their own and other cases implies that the basic lesion of interstitial fibrosis must be the result of viral infection or chemical irritation.

According to Peabody Jr , Buechner and Anderson, the most attractive hypothesis for cause of the disease is that which proposes a viral origin, but such a conclusion stems more from lack of evidence to support a bacterial *or occupational* etiology than from any positive evidence in its favor Thus, inclusion bodies have not been demonstrated and a virus has never been isolated. It is true, however, that occasional cases of primary atypical pneumonia will, in some areas, bear a resemblance to the Hamman-Rich syndrome In protracted or recurrent cases of influenza, somewhat similar histological changes are encountered. Therefore, its emergence from a variant form of these viral infections is a distant possibility

Kirshner, Breckenridge, Allbritten, and Theodos did not find an indication from the clinical course or from the laboratory or pathological studies of a bacterial infection or chemical irritation that might be responsible for diffuse interstitial fibrosing pneumonitis. The histological findings of diffuse interstitial fibrosis with extensive proliferation of connective tissue within the alveolar walls may represent a certain type of tissue response to some unknown virus

There is some evidence that this unknown agent attacks more readily persons of a certain genetic constitution. The occurrence of the disease in twins and brothers may implicate that the susceptibility to the assumed virus infection is part of a constitutional defect MacMillan thinks that there is a possibility that the lungs are the "Achilles heel" in certain individuals or families, and the basic etiological factor in familial pul-

thickness. The addition of collagen in such walls is variable; it may even be absent and is usually focal rather than widespread. Involvement of blood vessels was noted by Rubin, Kahn, and Pecker. The changes consist of mild to severe intimal thickening of the arteries, and at times, obliterations of the lumina. But it is difficult to distinguish whether the vascular changes are part of the disease or secondary to the hypertension of the lesser circulation which may lead to *cor pulmonale* in many cases.

Spain mentioned that the subintimal fibrous proliferation in smaller arterioles was frequently associated with alveolar fibrosis. Whether this is a part of a primary process or secondary to the fact that there is interference with the nutrition of blood vessel walls is not clear.

According to Peabody Jr., Buechner and Anderson, the pulmonary arterioles not infrequently show subintimal proliferation because pulmonary hypertension is a natural consequence of diffuse interstitial fibrosis.

Golden and Tullis, Katz and Auerback expressed the view that interstitial fibrosis of this type may be due to the failure of resolution and subsequent organization following one or more attacks of acute interstitial pneumonitis, socalled primary atypical pneumonia

Callahan, Sutherland, Fulton, and Kline stressed that the anatomic findings in their cases, as those previously reported by others, imply a single pathologic process with production of various physiologic disturbances. The fundamental pathologic change which consists of an increase in interstitial connective tissue leads to reduction of the pulmonary vascular bed, to impairment of the blood flow through the lungs. The subsequent development of interstitial edema and transudation of fluid into the alveoli interfered with the gaseous exchange and was responsible for clinical symptoms of dyspnea and cyanosis Peripheral emphysema in uninvolved portions results from hyperpnea and excessive respiratory effects. According to the above authors, the production of fibroblasts constitutes the response to the lymph in the intracellular spaces, it is usually associated with chronic obstruction to the lymph flow, and similar lesions have been obtained experimentally in subcutaneous tissue by producing obstruction in regional lymphatic channels Such a hypothetical sequence of events may be a factor in the development of the changes in the interstitial tissues of lungs This type of pathologic change could also explain the prodromal stage and the acute stage of the disease.

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monary fibrosis may be a familial response to pulmonary trauma of an organic (infectional) or inorganic nature.

Familial features in virus infections are well known. Thus, siblings and children of the same parents are more liable to be attacked by poliomyelitis irrespective of exposure, and Aycock spoke of familial aggregation in poliomyelitis; the cases of familial Hamman-Rich syndrome do not offer sufficient information.

Rubin, Kahn, and Pecker assume that not all instances of interstitial fibrosis of the lung are necessarily fatal. It was their impression that once the condition was recognized it proved less rare than generally believed and not so acutely progressive as was found in most cases reported.

Geever, Neubuerger, and Rutledge have demonstrated the histological picture of the Hamman-Rich syndrome confined to a single lobe, and it may well be that localized and non-fatal forms of the disease occur.

It appears probable that the chronicity of the process does not invalidate the diagnosis. The prognosis of diffuse interstitial fibrosis depends much on the degree of right-sided heart failure; but the course of the cardiac situation is determined to a great extent by the primary pulmonary disease It was generally impossible to change the pathologic process within the lungs. The prognosis is usually grave, and cardiac decompensation is progressive in spite of all modern treatment. Cor pulmonale is an impediment to coronary outflow and is often menaced by sudden death without immediate visible cause.

The usual treatment in advanced interstitial fibrosis of the lungs is bed rest, mercurial diuretics, ammonium chloride, digitalis, oxygen. Repeated venesections have been used. In cases with peripheral thrombophlebitis, anti-coagulant therapy and penicillin have been tried.

Brock finds that the diffuse interstitial fibrosis of the lung resembles that seen in experimental influenzal pneumonia of animals and suggests that Aureomycin or Chloromycetin should be administered and may perhaps be life-saving. But this advice is not based on personal experience.

According to Peabody Jr., Buechner and Anderson, the disease has stayed singularly unresponsive to all forms of therapy in every instance to date. Except for the administration of oxygen and symptomatic care, there is little the physician can do for these patients. On the basis of two deaths following cortisone withdrawal and a third following a slight decrease in corticotropin (ACTH) dosage, these authors question the

advisability of so treating any but the most desperate cases of diffuse pulmonary fibrosis. If the endocrinal agents are utilized, a permanent maintenance dose is advocated; should withdrawal be contemplated, the utmost caution is urged. One case of Silberman and Talbot also received cortisone for two months during the last stage of the disease. No significant benefit was obtained; fortunately the therapy was discontinued without incidence.

The etiology of the Hamman-Rich syndrome remains, for the present, unknown. However, the most captivating hypothesis is that which suggests a virus as the cause of the basic lesion, and it is because of this that the Hamman-Rich syndrome is included in this survey.

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2. Infectious Mononucleosis

The increasing interest in infectious mononucleosis (glandular fever), a disease mainly characterized by fever, lymphadenopathia, and sore throat, is reflected in the vast amount of publications which have appeared during recent years.

Many practitioners are still reluctant to make a diagnosis of infectious mononucleosis. The total effect of this disease on children and young adults and its potential harm in the individual patient is still underestimated (Houck).

If we try to compare the original concept of ill-defined idiopathic adenitis or glandular fever with the present-day concept of infectious mononucleosis, it appears that not only the terminology but also the definition of the illness has undergone certain changes. The present-day concept of infectious mononucleosis cannot be considered as final and has to be modified as further observations and improved laboratory methods necessitate it.

Infectious mononucleosis presents a chaos of events in disease as the clinical manifestations are variable in type and severity In addition to the acute and subacute type, the walking and chronic cases should not be overlooked. *Histologically, infectious mononucleosis is a generalized disease and produces changes in almost every organ, thus explaining the diversity of clinical manifestations.*

The opinion that infectious mononucleosis should be a peculiar individual response of a lymphatic constitution to a variety of infectious agents is obsolete. The majority of investigators believe that it is produced by a specific infection. Although its viral nature is probable, the demonstration of the causative agent and its transfer to other organisms has not yet been successful, but there certainly has been no lack of experiments.

The influence of concomitant or secondary bacterial infections in many cases of infectious mononucleosis cannot be overlooked

Infectious mononucleosis is a common disease with universal spread. It preferably attacks the younger population although the older age groups are not spared. Sporadic occurrence is more common than familial infection or circumscribed epidemics Infectious mononucleosis has a tendency to recurrences and relapses (Stevens, Bayrd, and Heck) Apart from the causative agent, a number of contributory factors must be taken

nto account. Occasionally, an infectious mononucleosis may follow other infections such as tonsillitis or pneumonia, which may furnish a predisposing factor and may reduce resistance. However, our attention should not merely be fixed to the causative agent, as the varying susceptibility of the host should also be taken into consideration.

In milder cases the patients have headache of variable intensity, weakness, fatigue, fever, enlargement of lymph glands, enlarged spleen, typical blood pictures, i e., presence of abnormal, large lymphocytes, and an increasing sheep-cell agglutinin titer, the Paul-Bunnell test.

The disease lasts for two to three weeks, but sometimes longer than one year. The convalescence is often slow. The clinical manifestations of infectious mononucleosis are variable in type and severity. The different types are the lymphoglandular type (generalized or partial lymphoglandular enlargement), the oropharyngeal type (monocytic angina, pharyngitis), the respiratory type (pneumonitis), the abdominal type (hepatitis, jaundice, an appendicitis-like picture, spleen rupture), a type similar to typhoid fever or brucellosis There are cases associated with skin eruptions, hemorrhagic manifestations, cardiovascular involvement (myocarditis, energetic-cardiac insufficiency, myocardosis, pericarditis), and involvement of the central nervous system and peripheral nerves.

Autopsy and biopsy findings have shown that lymphatic and reticulo-endothelial structures of the body are affected by the disease (Custer and Smith, Kalk and Ulbricht) Bone marrow puncture revealed either no abnormality at all or some increase in granulopoiesis Hovde and Sundberg found focal granulomas in the bone marrow. Lymph nodes showed monocytoid lymphocytes and lymphatic monoblasts in the cellular picture The lymphatic monoblasts are the source of the infectious-mononucleosis cells, i e , the abnormal lymphocytes in the blood. We are here dealing with reticulo-endothelial cells and monocytoid cells (Moeschlin)

A precondition for the diagnosis of infectious mononucleosis is that we should be acquainted with the characteristics of the infectious-mononucleosis cell and with the vagaries of immunologic phenomena frequently occurring in this disease. *It is not permissible to regard the infectious-mononucleosis cells of the blood as normal lymphocytes or monocytes or lymphoblasts.* The onset of an increasing sheep-cell agglutinin titer (over 1/80 or more) during the course of the disease varies exceedingly The rise and fall of this titer is often abrupt, but sometimes

it decreases slowly. In many cases of a typical infectious mononucleosis with typical blood alterations, the Paul-Bunnell test remains negative or low (1/16) in the first weeks; in many cases it may not be possible to repeat the test or to determine the maximum titer. It is a frequent event that a typical blood picture and a positive Paul-Bunnell test appear for the first time during convalescence. Without frequent examination of the blood picture and agglutination of sheep's erythrocytes, many cases escape detection. Special exclusion tests provide a differential absorption pattern to clarify a doubtful heterophil titer.

Liver involvement is often prominent with and without jaundice. Abdominal pain and tenderness in infectious mononucleosis is caused by enlargement of the liver, spleen, or mesenteric glands. Sharp abdominal pain and other symptoms often resemble appendicitis. Morbilliform, scarlatiniform, and other eruptions are frequently observed. Hematuria, hemorrhages into the skin, epistaxis, and hemorrhages from the rectum may occur. Thrombopenic purpura is occasionally observed. In the presence of cervical rigidity and other involvement of the central nervous system, differential-diagnostic problems are involved, and it is worth while to have Paul-Bunnell tests performed

Many authors have described electrocardiographic alterations in infectious mononucleosis According to Houck, there is the danger that minor electrocardiographic deviations may cause too much concern on both physician and patient and lead to unnecessary treatment. On the other hand, there are cases of infectious mononucleosis associated with cardiac and circulatory failure, cyanosis, and pericarditis, they show that cardiovascular involvement is not always a minor complication Not too severe cardiac disease in infectious mononucleosis may cause disability for some period of time, although recovery is the rule. Cardiovascular manifestations in infectious mononucleosis may be an important part of the disease or may be present only during a short and transient episode. Infectious mononucleosis as a generalized disease may produce organic changes also in the heart.

Pathologic observations of cardiac involvement in infectious mononucleosis have been made by Jersild (1942), Ziegler (1944), Allen and Kellner (1947), Brien (1947), Custer and Smith (1948), Dolgopol and Husson (1949), Kass and Robbins (1950), Stobbe (1951), Knick and Hoffmann (1953), and Klein (1954)

Jersild described the case of a 25 year old man with infectious mono-

nucleosis verified by a typical blood picture and increased titer of agglutinin for sheep erythrocytes The electrocardiogram showed depression of ST segments in lead 2 and 3. He died eight days after the onset of the disease. Myocarditis was the stated cause of death, but necropsy findings did not reveal outspoken myocardial involvement. Ziegler reported the case of a 22 year old woman with infectious mononucleosis. The heart revealed the acute changes "common to many infections," but no cellular infiltrations which were observed in the liver, kidneys, lungs, and spleen.

Allen and Kellner described the case of a 23 year old Air Force pilot who died 31 days after the onset of infectious mononucleosis. The heart showed focal collections of mononuclear cells and lymphocytes, the interstitial infiltrations seen in the heart were compatible with conductive changes demonstrable by electrocardiograms in this illness.

Similar findings are reported by Brien in two soldiers who died of rupture of the spleen.

Custer and Smith were unable to detect pericarditis in nine fatal cases of infectious mononucleosis. Cardiac lesions were found in six cases, while one case was doubtful. The foci were small in all but one where there were rather extensive residual areas of myocarditis (this case was already reported upon by Allen and Kellner). The small cardiac infiltrates they observed may explain the electrocardiographic alterations in infectious mononucleosis.

Dolgopol and Husson found, at necropsy of a 19 year old girl, moderate edema of the heart and loss of striation.

Kass and Robbins discussed the case of a 19 year old girl who died following rupture of the spleen They found focal collections of lymphoid cells in the heart. In the endocardial region and within many trabeculae carneae there were interstitial collections of typical and atypical lymphocytes.

Stobbe and Knick and Hoffmann observed, in their cases, small perivascular inflammatory foci in the heart, very similar to those observed in rheumatic myocarditis. These observations explain that myocardial interstitial infiltrations, mostly focal, represent the organic background for the electrocardiographic changes observed in infectious mononucleosis. They may occur in any part of the heart.

It is hard to estimate the incidence of cardiac involvement in infectious mononucleosis.

Contratto believes that cardiac changes observed in patients with infectious mononucleosis cannot be attributed to this illness. Wintrobe believes that cardiac symptoms are uncommon.

Leibowitz thinks that, in the light of predominance of cases without clinical evidence of cardiac involvement, it can safely be estimated on clinical grounds alone, the heart is very infrequently affected. If electrocardiograms are routinely performed, a higher percentage of incidence of involvement is revealed, varying from five to as many as forty per cent, but there is little or no correlation between electrocardiographic abnormalities and clinical findings pointing to cardiac disturbance. The correct interpretation of the electrocardiographic findings remains to be decided upon. However, the postmortem findings of focal interstitial infiltrations of abnormal lymphocytes in the myocardium are highly suggestive of the electrocardiographic changes being due to organic changes in the myocardium on an inflammatory basis.

No symptoms and signs referable to heart involvement are listed in a number of reports on infectious mononucleosis (Read and Helwig, Sturgis, Stevens, Bayrd and Heck, and many others)

Electrocardiographic studies are the main source of observed cardiovascular involvement on infectious mononucleosis Cardiac involvement in this illness is frequently found during routine electrocardiographic studies. Most commonly the abnormalities exist in minor changes of T waves, the prolongation of PR interval, premature beats, or some changes of the ST segment of the electrocardiogram Prolongation of PR in cases of infectious mononucleosis have been recorded by Logue and Hanson, Young, Lyon, abnormalities of T waves by Candel and Wheelock, Lyon, Young, Geraghty, Bennike, Schultz and Hall.

Wechsler, Rosenblum, and Sills (1946) performed electrocardiograms in 223 cases of infectious mononucleosis and found T wave changes in 39, prolonged PR intervals with and without T waves alterations in 14 There were two instances of transient second-degree heart block

Jaffe, Field, and Master found deviations in T waves in nine of 22 cases. In addition, the PR interval was prolonged in two patients. Occasional auricular premature contractions occurred in one case

Trautmann and Schennetten described atrioventricular interference dissociation.

Lyon (1950) reported three cases of infectious mononucleosis with electrocardiographic alterations; one case with auricular premature con-

tractions, one with T wave inversion, one case showing a late scarlatiniform eruption and prolonged PR interval. In the third case the cardiac involvement was assumed to be due to the activity of secondary bacterial invasion especially of hemolytic streptococci with resulting allergic inflammatory reaction in the heart. Additional functional alterations of the heart in the course of infectious mononucleosis cannot be excluded (Lyon, 1950, b).

Bennike summarized his observations in 166 cases of infectious mononucleosis and concluded that electrocardiographic changes occurring in the acute phase were of transient character The main changes were in the T waves

Kalk and Ulbricht found prolongation of PR interval, broad QRS complexes, lengthening of QT duration, depression of ST segments in leads 2 and 3, flattening of T waves in 12 of 25 cases. Lengthening of QT duration signifies an energetic cardiac insufficiency

Electrocardiographic abnormalities in infectious mononucleosis are mentioned by Koch, by Dieck and Maekelt, and by Klein.

Clinical studies of cardiac involvement in infectious mononucleosis add some features to the electrocardiographic findings Wintrobe already mentioned a patient in whom tachycardia and cyanosis was so pronounced as to suggest acute cardiac dilatation Lyon reported that patients suffering from infectious mononucleosis and showing electrocardiographic changes complained of precordial pain, slight breathlessness, asthenia In one case, only the cardiac complaints led to examination and to the discovery of glandular fever in a girl

According to Wechsler, Rosenblum, and Sills, abnormal cardiac findings were scanty in their cases associated with abnormal electrocardiographic findings Cardiac enlargement was demonstrable in three cases A faint systolic murmur was audible over the precordium in 22 cases. Premature contractions were noted in few cases. A bradycardia and sinus arrhythmia was always present after the fever had subsided One patient complained of sharp precordial pain

Kalk and Ulbricht found tachycardia, hypotension, systolic murmur varying in intensity, accentuation of the second sound at the pulmonary valve area. These authors believed that there may be in infectious mononucleosis a disease of the myocardium and perhaps of the endocardium.

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Several authors reported characteristic signs of acute pericarditis, the

friction rub over the precordium, or pericardial effusion or electrocardiographic changes suggesting pericarditis.

Evans and Graybiel reported four cases of infectious mononucleosis with electrocardiographic changes consisting of depression or inversion of the T waves. These abnormalities persisted for six to 41 days. The authors considered the T wave changes to be the result of pericardial involvement. In one case, a pericardial friction rub appeared on the fifth day of illness. In a fifth case, a 20 year old man had substernal pain radiating across the left side of the chest. The heart was moderately enlarged, the sounds were of poor quality, and a pericardial rub was audible in the third and fourth intercostal space to the left of the sternum. A diagnosis of pericarditis with effusion was made The electrocardiographic changes were: lowering of the T wave in the limb leads, and diaphasic T wave in CF_4 Evans and Graybiel suggested that the cardiac involvement in glandular fever was more of the pericardium than of the myocardium.

Boehm, Rose and Barnes noted in one case of infectious mononucleosis an electrocardiographic pattern suggesting pericarditis but did not hear a friction rub.

DeFazio and Marsico reported a case of infectious mononucleosis in a 42 year old man. Examination revealed a pericardial friction rub, x-ray evidence of cardiac enlargement, and serial electrocardiographic changes consistent with acute pericarditis.

Miller, Uricchio, and Philipps recorded three cases, in ages from 19 to 26 years, with hematologic and serologic evidence of infectious mononucleosis. A pericardial friction rub was audible in each case. It persisted from one to four days. Typical electrocardiographic changes of acute pericarditis appeared simultaneously In two cases the electrocardiogram showed transient elevations of the ST segments. The subacute stage pattern was characterized by T wave inversion, present in some or all of the standard and precordial leads. Serial roentgenograms of the heart revealed enlargement of the cardiac silhouette in two cases; this disappeared during the hospital course.

Leibowitz reported on a case observed by Kramer. The patient was a 24 year old man with proven infectious mononucleosis who developed acute pericarditis with effusion, confirmed by roentgenograms and by the classical electrocardiographic changes, i e., persistent elevation of the ST segments in the limb and precordial leads plus inversion of T

waves. There was no history of rheumatic fever. The patient made a full recovery over a period of several months.

Soloff and Zatuchni reported a case of a boy, 17 years old, in whom the first symptoms of infectious mononucleosis were those of acute pericarditis. If the lymphadenopathia had not been discovered, this case could have been regarded as one of acute, non-specific pericarditis. This boy had clinical and electrocardiographic evidence of acute pericarditis and, also, transient upper nodal rhythm. Serial electrocardiographic tracings showed the typical sequential changes of acute pericarditis. The last tracing taken four and a half months after the onset of illness was still not entirely normal. Clinically the patient was well.

Miller, Uricchio, and Philipps considered the pathogenesis of acute pericarditis in infectious mononucleosis and suggested several possibilities; i e, the proximity of the hilar lymph nodes with extension of the infection into the pericardial sac, a virus infection of the pericardium, or a response of the pericardium as a shock organ to an offending allergen in a sensitive person.

Clinical and electrocardiographic alterations in infectious mononucleosis are similar to those that occur in numerous infections. The presence of hemolytic streptococci has been frequently described in glandular fever Some early clinicians were of the opinion that a streptococcus was the etiological agent of the malady The frequent streptococcal infections associated with infectious mononucleosis are to be regarded as typical complications, and the possibility of a secondary bacterial invasion must be considered in cases of cardiac involvement in infectious mononucleosis.

Wechsler, Rosenblum, and Sills had records of throat cultures in 104 patients of infectious mononucleosis. Of these, 61 were negative and 43 positive. In 28 cases with abnormal electrocardiograms, 13 throat cultures were positive for *Streptococcus hemolyticus*. Serial antifibrolysin titers were performed in 23 cases with electrocardiographic alterations. In 16, there was evidence of the presence of antifibrolysin in the circulatory blood The antifibrolysin titer usually reached its height in three to four weeks and then gradually decreased. Positive throat culture for *Streptococcus hemolyticus* were not always found in those cases that showed a rising antifibrolysin titer.

In a study of 210 cases, Stevens, Bayrd, and Heck reported that in 22 cases hemolytic streptococci were cultured from the pharynx.

Bacteria other than streptococci may also become aggressive and complicate infectious mononucleosis.

In many cases of glandular fever, a transient granulocytopenia is noted either at onset or during the second, third, and fourth week of illness, i.e., in the acute stage of the disease lasting some period of time and sometimes extending into convalescence (Lyon, Alder, Koch, Pelner and Waldman; Dieck and Mackelt). Granulocytopenia may be responsible for a temporarily lowered resistance and may lead to secondary bacterial invasion of the heart

The question of a scarlatiniform eruption in infectious mononucleosis and its relation to myocarditis needs explanation. Wechsler, Rosenblum, and Sills emphasized that the nine cases of scarlatiniform rash among their infectious mononucleosis patients were indistinguishable from that of classical scarlatina.

The positive Schultz-Charlton test in every member of the group is difficult to explain on other grounds, and speaks against the possibility than an erythrotoxin is produced by the etiologic agent of infectious mononucleosis or some other secondary invader.

In eight of these patients throat cultures were positive for *Streptococcus hemolyticus*. There was sufficient evidence in support of the view that the scarlatiniform eruption was the result of the secondary invasion by *Streptococcus hemolyticus*

In infectious mononucleosis, associated with scarlatiniform eruptions, myocarditis may develop on the basis of a streptococcal infection. Myocarditis occurs early or later in the course of scarlet fever (Steinmann). The more frequent myocarditis occurs in the initial stage of scarlatina as a direct result of the scarlatinal streptococcal toxin and produces mainly T wave alterations of a transient character The late myocarditis does not appear until the third or fourth week of illness or even later, and is characterized by tachycardia, enlargement of the heart, and murmurs. Its course represents periods of improvement alternating with re-exacerbations. The prolongation of the conduction time is not found in the initial stage of scarlet fever As the cause of the late myocarditis two types of allergy are possible, one resulting from hypersensitivity to the infective agent itself, and the other occurring as the result of autoimmunization due to an adjuvant action of the infective agent (from autoantibodies of the heart) During the second phase of scarlet fever the antigen-antibody effect outweighs that of the specific toxin

Lyon (1950) observed a case of infectious mononucleosis in a female patient, 19 years old, (with leucopenia—2800 leucocytes on the third day of illness with the highest Paul-Bunnell test (1/640) on the seventh day of illness, on the same day 77 per cent mononuclear cells with 12.5 per cent abnormal lymphocytes) In the fifth week of illness a scarlatiniform rash appeared, and later typical desquamation occurred. Three weeks after the onset of the rash, subjective heart troubles developed without physical alterations of the heart. The electrocardiogram showed a PR prolongation of 0 22" and, four months later, its reduction to 0 2". This was a late myocarditis occurring on the basis of an allergic inflammatory reaction of the heart to a streptococcal infection.

The frequent electrocardiographic changes in infectious mononucleosis have up to now been attributed to myocarditis and/or non-specific derangement of the neuro-vegetative regulation of the heart In prolonged cases of infectious mononucleosis with liver involvement, electrocardiographic changes may also be related to liver impairment which leads to the hepatic-cardiac syndrome of myocardosis and may be associated with plasma protein changes

Lyon, Knick and Hoffmann suggest that infectious mononucleosis may produce myocardosis Knick and Hoffmann assumed that there was, in six cases of infectious mononucleosis, a diffuse myocardial damage, evidenced by electrocardiographic abnormalities and associated with plasma protein alterations Electrocardiographic alterations, especially minor changes, in infectious mononucleosis may be caused by drugs, fever, increased tonus of the autonomous nervous system, electrolytic disturbances, tachycardia, and the position of the heart and must be evaluated with caution (Jaffe, Field and Master). In infectious mononucleosis, lability of T waves has been observed in serial electrocardiograms Holzmann believed that unstable T waves taken from lead CF_2 were often produced by a mild infection In association with other diseases such as rheumatic fever, electrocardiographic manifestations may be present today and gone tomorrow because foci of new inflammation constantly light up and vanish (Scherf and Boyd)

Allergic manifestations within the heart in scarlatina show similar electrocardiographic changes The variability of electrocardiographic features—the waning and waxing of T waves—may be not only the sequelae of the coming and going of irritating foci but also of variable functional factors in the convalescent stage of infectious mononucleosis

There is unity of opinion that cardiac involvement in infectious mononucleosis is usually not severe and mostly transient. Cases of cardiac and circulatory failure in this illness are exceptions but occasionally need treatment with rapidly acting cardiac glycosides (Koch). Heart involvement is the cause of prolonged convalescence. The precept of rest for a longer period of time in cases of cardiac involvement is justified.

In infectious mononucleosis, the frequent granulocytopenia may facilitate a secondary bacterial infection. Some authors suggest penicillin to tide these patients over that granulocytopenic period. According to Joyce, Pelner and Waldman, penicillin is an important part of the treatment of the complicating sore throat in infectious mononucleosis. Patients with myocardial involvement, oropharyngitis, angina, and hemolytic streptococci in throat cultures in infectious mononucleosis should be treated with antibiotics (penicillin, Aureomycin, Chloromycetin, Terramycin).

In order to prevent additional granulocytopenia caused by some modern antibiotics and sulfa drugs, folic acid, nucleoproteids, or even blood transfusions have been recommended. In cases of allergic myocarditis associated with scarlatiniform symptoms in infectious mononucleosis, the treatment consists of the use of one of the antihistamine drugs (Pyribenzamine, Benadryl).

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3 Epidemic Hemorrhagic Fever

Epidemic hemorrhagic fever, a strange, often fatal disease of unknown etiology, is characterized by sudden onset with intense headache, fever, chills, marked thirst, vomiting, widespread capillary damage, hemorrhagic diathesis, oliguria, and albuminuria. This fever has been known to exist in the Russo-Manchurian regions, adjacent Siberia, and in Korea.

According to Hullinghorst, the disease is thought to be due to a virus harbored in field rodents and transmitted by an arthropod vector. Pruitt and Cleve are also of the opinion that the disease is presumably of viral etiology and transmitted by bite of a mite or a tick. Many of the manifestations of the disease suggest rickettsial involvement, although rickettsias have not yet been isolated. Others believe that the clinical picture is more suggestive of a leptospiral infection. The mortality of the military cases in 1951 was approximately seven per cent, but since it has been slightly less than five per cent (Smyth and Powell).

Epidemic hemorrhagic fever involves every system and organ in the body. The cardiovascular system commonly shows pathological changes.

The incubation period is from two to three weeks, but may last 35 days, followed by three fairly well defined stages; (1) the invasive, (2) the toxic, and (3) the convalescent phase. Others divide the clinical course into four phases each designated for a characteristic aberration; (1) febrile, (2) hypotensive, (3) oliguric, and (4) diuretic. In the invasive (febrile) stage, which lasts three to five days and ends with toxic manifestations of the disease, a relative bradycardia and a dicrotic pulse is present. The blood pressure is usually normal for the first few days, but then it may drop to near shock—or even shock—levels. The symptoms may become intensive between the third and the seventh day of illness. Severe shock has also been correlated with a prolonged acute phase. Hemorrhagic manifestations start about the third day of illness and last three to eight days Renal disease starts on the third to sixth day of illness and resembles lower nephron nephrosis The second or toxic (or hemorrhagic) stage usually begins just before the fever subsides and continues until the tenth to fourteenth day of illness, occasionally longer. There may be a tachycardia and at times a sinus bradycardia. Some patients show cardiac dilatation and myocardial failure There are faint heart sounds. The blood pressure may drop; the pulse may be rapid and of poor quality. Pulmonary congestion may occur. Dyspnea and cyanosis may accompany the hypotensive stage Death during this stage may have a cardial basis from myocardial failure, hyperpotassemia, and ventricular fibrillation.

Early in the convalescent stage, beginning about the tenth to fourteenth day of illness, the blood pressure tends to be elevated (during the oliguric phase of the disease) but usually to return to normal later (during the following polyuric period) An orthostatic hypotension may be observed for several weeks The convalescent stage may last from six weeks to four months. The chief manifestations are polyuria and inability to concentrate the urine Diuresis may lead to transient salt and potassium loss.

The electrocardiograms observed in epidemic hemorrhagic fever show no consistent changes During the toxic stages, the T waves may become inverted, even deeply in all leads especially in the precordial leads. The T wave changes are slow to return to normal Hyperpotassemic alterations occur with renal failure According to Barbero, Katz, Kraus,

and Leedham, sinusbradycardia was observed during the first three weeks of illness, but sinustachycardia sometimes appeared during the second week or later. Second-degree heart block was seen during the first weeks of illness. The QT interval was prolonged during the second and third week, it ranges from 0.44" to 0.48". The prolonged *electric systole* appeared during the period of maximal renal failure or in the period of polyuria. Electrolytic disturbances could have accounted for these changes. Hyperpotassemia, hypopotassemia, hypocalcemia, hyponatremia, and hypernatremia have been reported (Hunter, Yoe and Knoblock).

Smyth and Powell observed electrocardiographic abnormalities or suggestive abnormalities in one or more tracings of 27 among 55 cases in the acute stage of hemorrhagic fever. A hyperkalemic effect was the most common change noted, since its presence was indicated or suggested in 17 cases. It was, in general, related in timing and frequency to the oliguria and resultant azotemia. A prolonged QT interval was noted in eleven cases during oliguria and in four during diuresis. Sinus bradycardia was noted in four cases and multiple auricular premature beats in one. Non-specific negative T wave abnormalities, usually mild and transient, were noted in nine cases. One case each of left and right bundle branch block was observed. One case of R-ST segment elevation due to uremic pericarditis was found. Electrocardiograms were abnormal in six of seven fatal cases. Five of the six cases with abnormal tracings showed some evidence of hyperkalemia. Seven of 78 cases in the convalescent series showed deviations from normal. In four the changes were slight; the other three included right bundle branch block, auricular fibrillation, and T wave inversions.

According to Pruitt and Cleve, the basic pathologic lesion in epidemic hemorrhagic fever appears to be a diffuse capillary damage (widespread, non-inflammatory disorder of capillary circulation) with capillary dilatation, increased capillary fragility or permeability of the vascular system with hyperemia, and small or large purpuric or ecchymotic hemorrhage, often with free bleeding or oozing of blood on the surface. This produces a marked disturbance in the peripheral circulation with hemoconcentration, hypotension, and inadequacy of the circulating blood volume. According to Beard, the outstanding pathologic feature is a pronounced disturbance of peripheral circulation with paralysis of the capillaries causing stasis and transudation, and later, spread to larger vessels.

According to Earle, widespread abnormalities of small blood vessels appear to be the chief characteristics of the early phases of hemorrhagic fever and set the stage for subsequent developments. Arteriolar dilatation occurs during the febrile and hypotensive stage. Plasma is lost through damaged capillaries and erythrocytes are pooled and trapped in dilated capillaries. This process can produce shock and can impair circulation in certain organs and areas, even in the absence of hypotension or shock. Hemorrhagic manifestations are capillary in origin and associated with thrombocytopenia. Plasma loss and arteriolar dysfunction are self-limited in duration, and for unknown reasons, the sequestered plasma may rather abruptly return to the vascular system and active circulation. But several features developing in the hypotensive phase may persist in the later stages In the oliguric phase, impaired renal function, oliguria, and electrolyte abnormalities dominate in certain patients, hypertension develops, and some patients exhibit a hypervolemic syndrome. The latter may occur even though the circulating blood volume may be less than normal and should, therefore, be termed "relative hypervolemia." Continued trapping of erythrocytes in dilated capillaries along with dehydration not only is responsible for the reduced circulating blood volume but also for a reduction in blood flow to various organs and for a contraction of available vascular space, which together furnish the basis for the development of "relative hypervolemia." In the diuretic stage there may be a "limited homeostasis" not unlike that seen in children suffering from diseases that produce fluid and electrolyte deficiencies.

Although no specific vascular lesion has been found in fatal cases of hemorrhagic fever, the pattern of the pathologic changes strongly suggests that vascular damage constitutes the basic disease process (Lukes). The heart is flabby with petechial involvement, but there is no valvular or coronary damage It is dilatated and soft with a relatively common finding of hemorrhages into the wall of the right, less often of the left, atrium. There may be interstitial edema, focal necrosis in the myocardium, endocardium, and epicardium with or without hemorrhage, but the ventricles may be less involved than the atria According to Hullinghorst, focal myocarditis and endocarditis occur, but the heart is usually the site of numerous hemorrhages, particularly of the right atrium. The myocarditis is evidenced by an interstitial infiltration of mononuclear cells which is most prominent in the left atrium and ad-

jacent portions of the ventricles becoming less so towards the apex. In no instance were these changes sufficiently marked to suggest the myocarditis of diphtheric type described in the Japanese and Russian literature reviewed by Mayer (Lukes).

In fatal cases, death is frequently due to shock in early stages and to uremia later. Of 61 deaths reported by Hullinghorst and Steer, 12 were due to shock and 28 due to uremia.

Pruitt and Cleve emphasized that the management of the shock or the hypotensive state is directed toward maintaining an effective blood pressure without overloading the patient until the integrity of the cardiovascular system is restored. Maintenance of electrolytic balance is important

Katz, Leedham, and Kessler recommended, for the therapy of the shock phase, careful handling and atraumatic evacuation, conservative fluid management based on detailed intake and output records, treatment of shock with Trendelenburg position, elastic bandage on the lower extremities, vasoconstrictors, and concentrated human albumin. Plasma, whole blood, and dextran have also been used.

Therapy directed towards correction of the diminished plasma volume by injection of concentrated serum albumin has been of great value but is sometimes inadequate (Katz, Leedham and Kessler; Yoe and Knoblock).

All available antimicrobial agents and many other drugs had no clinical benefits.

According to Smadel, in many instances conservative treatment of shock is sufficient, and the episode passes after a few hours. In those individuals with protracted hypotension and progressive shock, plasma expanders, especially concentrated albumin, and vasoconstrictors are used cautiously and in relatively small amounts. The usefulness of noradrenalin is being determined currently Experience has shown that the enthusiastic treatment of these patients in shock with large amounts of fluids has prompt untoward effects.

According to Yoe, hypotension and shock occurring during the hypotension phase of hemorrhagic fever responds at least transiently to continuous infusion of L arterenol. Decreased circulating plasma volume is an important factor in the etiology of the shock, and the judicious use of L arterenol and concentrated human serum albumin, either alone or in combination, appears to be the method of choice for the management of the severely ill patient in this phase of the disease

Earle emphasizes that, where loss of plasma from the vascular system and arteriolar dysfunction produce shock which does not respond to simple measures, concentrated human serum albumin and continuous intravenous administration of pressor drugs are the most effective therapy. Excessive administration of fluid must be avoided during the febrile and hypotensive phases since the added fluid leaks out of the damaged capillaries and thus increases edema and symptoms.

Problems of the oliguric and diuretic phases are concerned with fluid and electrolyte abnormalities. Phlebotomy is indicated for the hypervolemic syndrome, especially when associated with convulsions or marked mental agitation. Careful adjustment of fluid intake to urinary output is important during the early diuretic period.

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PART THREE

CHAPTER XI

Pathology and Clinical Features of Rickettsial Infections, with Special Reference to the Cardiovascular System

The rickettsial diseases of man are divided into five main groups: (1) typhus fever, (2) spotted fever, (3) tsutsugamushi fever (scrub fever), (4) Q fever, (5) trench fever.

Two varieties of the typhus fevers of group 1 are recognized; the epidemic, classic, louse-borne typhus, and the endemic, murine, flea-borne typhus Brill's disease is recrudescent epidemic typhus. The spotted fever of group 2 consists of Rocky Mountain spotted fever, boutonneuse fever, rickettsialpox The tsutsugamushi fever of group 3 is also known as the mite-borne typhus, scrub typhus, China fever, Japanese river fever, Burma eruption fever Q fever (group 4) has to be placed in the group of rickettsial diseases although it differs in many ways from the other members of the group Trench fever (group 5) is considered as a rickettsial disease, Mooser and Weyer (1953) successfully inoculated Rhesus monkeys with several strains of *Rickettsia quintana* and produced a long lasting rickettsemia in these animals

In cross-infection tests, animals recovered from infection with either epidemic (*Rickettsia prowazeki*) or murine (*Rickettsia mooseri*) typhus rickettsiae are more or less solidly immune to reinfection with both the homologous and the heterologous strains Cross infection experiments have also shown that infection with one strain of spotted fever rickettsiae will protect animals against reinfection with the homologous strain or a heterologous strain of the same group Some cross immunity between Rocky Mountain spotted fever and both epidemic and murine typhus is demonstrable (Rose)

With the exception of Q fever, the transmission of rickettsial maladies requires an arthropod vector.

RICKETTSIAE PATHOGENIC FOR MAN

Species	Disease
Rickettsia prowazeki	epidemic typhus
Rickettsia prowazeki	Brill's disease
Rickettsia mooseri	endemic typhus
Rickettsia rickettsi	Rocky Mountain spotted fever
Rickettsia tsutsugamushi	tsutsugamushi fever
Rickettsia conori	boutonneuse fever
Rickettsia burneti	Q fever
Rickettsia quintana	trench fever

Q fever, trench fever, rickettsialpox differ much from typhus fever, spotted fever, and tsutsugamushi fever which are clinically and pathologically similar to one another. The combination of vasculitis, hyaline thrombi, nodular and diffuse accumulations of mononuclear cells, myocarditis, myositis, and nodules in the central nervous system is probably diagnostic of typhus, spotted fever, and scrub typhus (Wartman).

These rickettsial diseases are primary infections of the blood with secondary focal infections of small vessels, they present similar clinical features and show great variations in severity.

Q fever, while usually a benign infection, may occasionally be fatal. Trench fever is not regarded as a serious disease but may often be a disabling illness Rickettsialpox has been included in the spotted fever group but has certain immunological and clinical differences, it should be regarded as a distinct member of group 2.

Susceptibility to rickettsial diseases is common; every infection leads to disease, the organism reacting in the characteristic manner under the particular conditions of the various rickettsial infections. Many of the symptomatic manifestations and pathologic changes in patients from rickettsial diseases cannot be accounted for by direct invasion of tissues by rickettsias, and therefore, must be ascribed, at least in part, to the action of toxic components of the microorganisms (Allen and Spitz, Rose).

An eschar is present at the site of the primary skin infection in most cases of scrub typhus, boutonneuse fever, South African tick bite fever, and rickettsialpox.

Mortality is high in epidemic typhus of adults but low in murine typhus, nil in boutonneuse fever, Brill's disease, and rickettsialpox. Case fatality is low in Q fever, nil in trench fever

Pathology of Rickettsial Diseases

It is not easy to distinguish epidemic typhus fever from Rocky Mountain spotted fever and tsutsugamushi disease on the basis of an objective study of the lesions. Allen and Spitz, Wolbach, Karsner, Wartman have reported affections of the cardiovascular system in their studies of these diseases, the essential or distinctive pathology of the rickettsial maladies is damage of small blood vessels especially in the skin, the subcutaneous tissues, the central nervous system, etc. Some points of these investigations may be mentioned in greater detail.

Damage of capillaries and blood vessels of precapillary size in the skin are responsible for the eruptions of the diseases. In Rocky Mountain spotted fever, the rickettsiae can be demonstrated fairly easily in sections of the skin; it is more difficult to demonstrate *Rickettsia prowazeki* of epidemic typhus, and in scrub typhus no attempt has been made for the demonstration of rickettsiae in the skin.

The first reaction of the rickettsial infection consists of the swelling of vascular endothelium. As a result of the intimal involvement, thrombosis occurs early. Vascular lesions are least severe in scrub typhus, and most severe in Rocky Mountain spotted fever in which the media may be directly injured in contrast to both epidemic and scrub typhus in which it is almost spared

There is a correlation between the eruptions of the three diseases and the degree in severity and distribution of the vascular lesions. In scrub typhus, petechial lesions are very usual and abundant, necroses are of relatively rare occurrence In Rocky Mountain spotted fever, petechiae are most abundant and necrosis seems frequent as the result of necrotizing lesions of vessel walls In Rocky Mountain spotted fever, the sites are not determined by pressure, while in typhus, necroses of the skin and subcutaneous tissues develop only in regions subjected to pressure as over bony prominences In all three diseases, lesions of blood vessels of the viscera correspond in severity with those of the skin and the subcutaneous tissue, least in scrub typhus, greatest in Rocky Mountain spotted fever Lesions of blood vessels may be found in any tissue and organ.

In all three diseases, pathologic findings of the central nervous system are present They take origin in capillaries, arterioles, and venules. There is infiltration of leptomeninges, perivascular accumulation of cells, sharply circumscribed lesions (nodules of miliary or submiliary size),

and some degree of cerebral edema. Circumscribed perivascular accumulations are found wherever vascular lesions occur. Rickettsiae have been demonstrated in cells of the accumulations in Rocky Mountain spotted fever and in typhus.

The infiltrations of organs, i.e., heart, lungs, liver, kidneys, are diffuse because of their relationship to capillaries. Associated with them are changes in the endothelial cells of capillaries, swelling, mitoses, and often thrombosis. Such diffuse infiltrations are more conspicuous in scrub typhus than in the other two diseases. The descending order of degree of cardiac involvement is scrub typhus, epidemic typhus, and Rocky Mountain spotted fever. According to Wolbach, in none of the diseases is there much evidence of degeneration of the heart muscle, and the importance of this "myocarditis" in relation to cardiac function is problematic, but Allen and Spitz emphasized that, in view of histologic changes in the rickettsial diseases, it would be justified to consider the contributing effect particularly of the heart, the kidneys, and the adrenals. Wolbach maintained that the fall in blood pressure or circulatory collapse, which is an outstanding clinical feature of rickettsial disease, is generally conceded to be the result of changes in peripheral circulation The hypoproteinemia which is a feature of all these diseases should be considered as an additional and perhaps important factor.

In the lungs, compression and blockage of the alveolar capillaries as well as accumulation inside as well as outside the capillaries occurs. In tsutsugamushi fever, the process is most marked, in epidemic typhus it is negligible. In scrub typhus and, to a lesser degree, in Rocky Mountain spotted fever, the result warrants application of the term "interstitial pneumonitis"

Wolbach described reactions of the liver, the kidneys, the adrenal cortex, and other organs and tissues He regarded the liver involvement as important in relation to liver physiology, particularly in the light of the hypoproteinemia of these diseases It appears that this hypoproteinemia is mainly caused by the capillary syndrome, i e, by escape of protein through the damaged capillary walls Histologic evidence of slight damage to the kidneys is present

Many clinical features observed in the three diseases are based on extensive involvement of the capillaries of the skin and other organs, but myocardial involvement in rickettsial diseases may play an additional role in many cases. Reports of fatal cases, prepared by the United States

of America Typhus Commission in Cairo, Egypt, during 1943-45 (Committee on Pathology, Division of Medical Science, National Research Council with collaboration of the Armed Forces Institute of Pathology), offered new information concerning involvement of the cardiovascular system in epidemic typhus. In this study, Karsner emphasizes that in epidemic typhus capillary injury is conspicuous. In part, it is without morphologic change and is evidenced by hemorrhage as an indication of fragility or by edema or protein precipitation in the subcapsular space of renal glomeruli as an indication of increased permeability. Swelling and proliferation of capillary endothelium are especially noteworthy in the dermis but occur elsewhere Usually this change is accompanied by pericapillary cellular infiltration Arterioles and venules may be similarly affected though not so frequently as the capillaries Arteries of medium size occasionally exhibit cellular infiltration in their intima, media, or adventitia, but only rarely is there necrosis of the wall Large veins may show cellular infiltrations of the intima and thrombosis. Occasionally the intima of the aorta is the seat of cellular infiltrations, rarely the adventitia In all cases, there is an associated myocarditis. Interstitial myocarditis of slight, moderate, or profound degree is constant There was no satisfactory evidence in favor of amelioration or healing of the myocarditis in patients who were febrile up to 18 days Infiltration of mononuclear cells is frequent in the epicardial fat and endocardium and less frequent in the connective tissue of the epicardial tissue According to Karsner, the clinical significance of the myocarditis is not well understood, at first it was thought to be the cause of circulatory collapse, but recently other explanations have been offered Wolbach is of the opinion that diffuse involvement of the endothelium is of importance in the production of physiological disturbances (dehydration, loss of electrolytes from the circulation, fall in plasma volume, and peripheral collapse). German authors thought that the cardiovascular manifestations of the disease were due to involvement of blood vessels in the vasomotor centers of the brain, and that the effects of myocardial injury become apparent only late in the course of the disease According to Wartman, the myocardium was commonly affected in the fatal Cairo cases of epidemic typhus Although most authors have been unable to show a good correlation between symptoms and myocardial lesions, the contributory effect of cardiac damage in severe and fatal rickettsial diseases is recently again being more and more emphasized.

Clinical Features of Rickettsial Diseases, with Special References to the Cardiovascular System

In epidemic typhus, Rocky Mountain spotted fever, and scrub typhus, malaise, pain in the back and in the limbs, headache, eruptions are observed. The pathology of these diseases shows general vascular involvement. According to Woodward and Bland, previous descriptions of epidemic typhus frequently refer to cardiac collapse, cardiac failure, or cardiac weakness, and little mention has been made of peripheral circulatory weakness with minimal stress as a possible explanation or of the fact that this factor may play the major role. The "heart per se" has been considered as the real cause for this very apparent deficiency.

An over-all review of clinical features, cardiovascular, biochemical, and other findings in severe cases of epidemic typhus, Rocky Mountain spotted fever, and scrub typhus gives indication of circulatory damage and also of cardiac involvement.

For this occasion, it appears undesirable to relate all particular clinical details for each of the three diseases; it would seem sufficient to integrate the observations of all three diseases into one picture showing circulatory deficiencies and myocardial involvement of severe cases.

In severe epidemic typhus, Rocky Mountain spotted fever, and scrub typhus, minor abnormal cardiac signs occur in the first week of illness. The size of the heart is normal, only exceptionally is there cardiac enlargement. In the second week, abnormal cardiac signs may develop. Heart sounds are poor in quality, there is softening of the first heart sounds, and systolic basal or apical murmurs are observed. The heart may be slightly enlarged. The pulse is first full and strong, then it becomes feeble, thready, rapid, irregular There may be also brief periods of ectopic heart beats. Occasionally the pulse becomes slow in comparison to the temperature. The heart may also develop gallop-rhythm or marked bradycardia The blood pressure is usually normal at onset, but later a persistent hypotension for variable periods is frequent during the acute stage of the illness Venous pressure is low or normal Electrocardiographic alterations are sometimes observed in epidemic typhus, i e, flattening or inversion of T waves, depression of the ST segment, PR prolongation, low voltage of QRS complex. There is no distinctive electrocardiographic pattern attributable to severe typhus. The abnormalities rarely persist longer than for a few months and usually return to normal. In scrub typhus, electrocardiographic changes consist of flattening of T

waves, ST elevations, bundle branch block, auricular fibrillation, complete A-V block. Most of these abnormalities disappear some time after recovery. In Rocky Mountain spotted fever serial electrocardiograms reveal some alterations (changes in T waves, rarely prolongation of PR intervals).

Peripheral cyanosis and cold sweat are present in severe cases of the three diseases.

Rhonchi or rales are heard over the lower lobes of both lungs and roentgenograms of the chest often demonstrate abnormalities ranging from hazy infiltration to patchy densities of the lungs.

Erythrocyte counts, hemoglobin, and hematocrit demonstrations do not show great abnormalities; moderate reduction during the course of the diseases are frequent Severe anemia is unusual.

The urine is reduced in amount; in fatal cases there may be anuria. Albuminuria may be present The deposits may contain erythrocytes, granular and/or hyaline casts

Involvement of the central nervous system is usual.

Variable degrees of hypochloremia, and moderate to significant azotemia is observed in severe cases Plasma carbondioxide is within normal limits except at the height of the disease in severe cases when it may fall to between 30 and 50 volumes per cent. There is a tendency for serum albumin to decrease as the disease progresses, particularly in severe cases. The serum globulins are increased leading sometimes to reversal of the albumin/globulin ratio Serum albumin may fall below 2.5 per 100 cc. late in the first week of disease, continue during the second and third weeks of severe rickettsial disease, and remain below normal for some weeks more. There is a normal blood volume early in the disease. A transient reduction of the circulatory blood volume at the clinical peak of the three diseases is present in severe cases. It returns to normal during the time of lysis In mild or moderately severe cases, the blood volume is not significantly altered.

Schittenhelm emphasizes that myocarditis is a rare occurrence in epidemic typhus and that the cardiovascular disturbances are of peripheral origin. In every case of epidemic typhus hypotension *follows the onset* of the disease

Woodward and Bland concluded from a laboratory and clinical study of 30 patients with severe epidemic typhus that the altered physiologic state, owing probably to widespread endothelial damage, consists pri-

marily of an inadequate circulatory blood volume, hypoproteinemia, especially decreased albumin fraction, hypochloremia, hemodilution without blood destruction, and azotemia. The circulatory collapse which is frequently encountered is of a primarily peripheral origin. Lowered blood volume means less adequate filling of the heart during diastole, and hence lowered cardiac output. The unstable circulation results in a reduction of renal plasma pressure, and hence, oliguria and anuria may develop General supportive measures to increase the circulating blood volume are recommended as very beneficial.

Wartman, in a general comment on the pathology of epidemic typhus, in the report of fatal cases studied by the United States of America Typhus Commission in Cairo, Egypt, during 1943-45, paid special attention to the problem of circulatory failure in this illness He emphasizes that the circulatory failure may occur during the acute stage of epidemic typhus and is often indicative of impending death. The extremities become cold and cyanotic The arterial blood pressure drops to low levels, and the arterial pulse becomes feeble and rapid Shock, hypochloremia, azotemia, lowered plasma volume, and increase in acid ions have been reported. This type of failure has been called "peripheral vascular failure." Congestive heart failure is very rare either in the acute stages of the disease or during convalescence except in moribund patients and is not relieved by digitalis. Electrocardiographic changes rarely persist longer than four weeks The explanation of this peripheral vascular failure is unknown It has been attributed to extensive involvement of capillaries of the skin and other organs, to injury of the vasomotor centers in the brain, to injury of the adrenal cortex with resulting adrenal insufficiency, to involvement of lungs and kidneys, and to myocardial injury. The latest studies of epidemic typhus have favored the first two explanations, or a combination of them, and have minimized the myocarditis. However, in view of the constant and often severe myocarditis in the fatal Cairo cases, Wartman does not regard the factor of myocarditis so lightly.

According to Harrell and Aikowa, peripheral circulatory failure is an important complication of Rocky Mountain spotted fever The plasma volume is reduced in the second week of the disease, and collapse may occur in the same week The peripheral collapse is accompanied by a decrease in serum proteins and by the development of edema

According to Harrell, it is not known how much protein escapes from

the vascular tree through the capillaries in the course of Rocky Mountain spotted fever Regardless of whether the fluid goes into the tissue spaces or the cells, the loss from the circulatory intravascular fluid lowers the blood volume and precipitates peripheral circulatory collapse.

Harrell, Venning, and Wolff maintain that, because of the vascular lesions, the loss of circulatory blood fluids, particularly protein, in Rocky Mountain spotted fever is analogous to that in burns. The administration of saline solution or glucose without blood or plasma will aggravate rather than correct the abnormal physiology by washing out further protein

Harrell stresses the fact that reduction in the circulatory serum proteins, especially in the albumin fraction, lowers the intravascular osmotic pressure and sets the stage for the subsequent development of peripheral circulatory weakness and collapse. In addition, damage to the liver may reduce synthesis of new protein so that replenishment is decreased and destruction is increased simultaneously According to Harrell, the alteration in capillary permeability is corrected when recovery begins; the blood volume is quickly restored to normal within one or two days after the temperature has dropped, and the toxemic symptoms decrease though the loss of edema may take as long as a week, and the restoration of circulatory blood proteins, even longer

According to Blake, although autopsy studies have shown that variable degrees of myocarditis are present in fatal cases of scrub typhus and suggest that it occurs to some extent in most cases, it would appear that the phenomenon of circulatory failure seen in severe cases is predominantly of peripheral origin rather than due to heart failure per se. Smadel believes that myocarditis occurring in scrub typhus patients and proceeding to permanent heart damage may be overemphasized But the same author mentions the fact that myocarditis of focal and diffuse distribution of varying intensity may be present Vascular changes with resultant lesions in adjacent parenchymatous tissues are most conspicuous in the heart A clear correlation between electrocardiographic alterations and mortality is not present Permanent cardiac damage in scrub typhus is rare.

In mild and moderate cases of epidemic typhus, Rocky Mountain spotted fever, and scrub typhus, the cardiovascular system, the central nervous system, and the kidneys appear to be less severely involved. Symptoms and signs are similar to those described in severe cases but

fragmentary. On the other hand, endemic murine typhus, one of the benign rickettsial diseases with usual recovery, may in the rare severer cases offer a picture similar to that of the severer epidemic typhus.

Woodward stresses the fact that the clinical evidence of cardiac failure as manifested by gallop rhythm, enlarged heart, engorgement of the neck veins, orthopnea, hepatic enlargement, ascites, and edema is lacking in endemic typhus. But the pulse may be accelerated; hypotension may be persistent during the acute stage of the disease. General vascular weakness is suggested by peripheral cyanosis and sweating. The specific pathological lesion consisting of widespread, minute endovasculitis certainly contributes more largely to these changes by way of diminished vascular tone than by cardiac failure per se. Minimal aberrations may be observed in the electrocardiogram which suggest myocardial involvement. These changes are transient. Thrombosis of larger vessels may be observed, particularly in the femoral, mesenteric, or brachial veins. The hematocrit is altered; sufficient hydration often produces a slight decrease (35-42 volume per cent in the volume of packed cells). Moderate albuminuria occurs. Cellular elements including casts are usually not found. Diminished serum chlorides, a reduction in serum albumin (2.2 mgs/100) have been observed in severely ill patients. There may be moderate azotemia in murine typhus. In the rare fatal cases, death may be due to general vascular failure with accompanying azotemia.

In Brill's disease, persistent hypotension during the acute stage of the disease, abnormal electrocardiograms lasting into convalescence, albuminuria, and oliguria as remainder of the general vascular involvement of a rickettsial infection are frequently present.

Therapeutics

The status of the rickettsial infections has changed since the advent of broad-spectrum antibiotics. The value of convalescent serum is doubtful. Sulfonamides are harmful. Penicillin failed. Aureomycin and Chloromycetin act mainly as rickettsiostatic agents, full recovery depends on the development of the immunity of the patient. Relapses may occur if antibiotics are discontinued before an adequate immune state has been attained. Many cases of epidemic typhus have been cured by Aureomycin; the temperature became quickly normal, and other clinical signs of the disease regressed though more slowly. Convalescence was shortened.

Chloromycetin and Aureomycin are considered effective in murine typhus. A large number of Rocky Mountain spotted fever cases have been treated with Aureomycin, Chloromycetin, and Terramycin. If the patients are not seen until after they have been ill for a week, Aureomycin treatment should begin intravenously. Chloromycetin and Terramycin are superior to any previous remedy. In other rickettsial diseases, the broad-spectrum antibiotic treatment has been successfully used. Although rickettsial diseases can now be controlled by antibiotics, management of cases cannot be confined to these drugs alone.

The precondition for a rational course of therapy is the knowledge of laboratory data of these diseases. This concerns the serum proteins, especially the serum albumin fraction, the blood non-protein nitrogen, and the urinary findings. The management of epidemic typhus, as explained by Yeomans in 1948, remains also today useful and may be briefly summarized. In the supportive treatment of typhus fever, diligent nursing care is a necessity not only during the febrile period but also during convalescence. Complete bed rest is obligatory during the acute phase of the disease Except in the presence of edema, the fluid intake should be regulated as to produce a 24-hour urine output of 1500–2000 cc. The frequent oral administration of fluid throughout the 24 hours prevents excessive dryness of oropharyngeal mucous membranes. Parenteral fluid administration should be resorted to with certain precautions when oral fluid intake is difficult or impossible.

The diet should be of high caloric value, adequate in vitamins, and of high protein content In patients with low chlorides, inclusion of 6–10 Gm of salt in the daily diet will rapidly raise the level of chlorides.

Digitalis and other cardiac drugs have no place in the supportive therapy of epidemic typhus unless indications for their use are present. Congestive heart failure is seldom found in this disease. But the use of digitalis, strophanthin, or ouabain in peripheral vascular collapse has never been of demonstrable value The duration of severe hypotension with oliguria is variable and depends, to a considerable extent, on supportive therapy. The usual period is one to four days. During this time, supportive therapy is most profitably directed toward prevention of a further drop in blood pressure, and this is best accomplished by the intravenous use of plasma, isotonic albumin solution, or whole blood. Saline solutions are contra-indicated in these patients. The serum albumin is

reduced and the administration of crystalloids often results in appearance of edema. The effect of plasma or albumin solution on the blood pressure is not long-lasting; it must be given frequently. It has been found that if, by their use, one can prevent the onset of peripheral collapse, the patient may be supported through a most critical period of his disease. The first indication of an improvement in these patients is a rise in blood pressure.

According to Harrell, if the plasma proteins in Rocky Mountain spotted fever are found to be low or falling rapidly, or if an appreciable drop in systolic or diastolic blood pressure gives evidence of impending circulatory collapse, preformed protein should be administered Intravenous replacement in the form of purified albumin, plasma, or whole blood increases the intravascular osmotic pressure enough to allow crystalloids to be given safely. A very large amount of preformed protein may be required to restore to normal the circulatory blood volume and blood constituents. ecause of the possibility of myocardial damage, the quantity and speed of administration of parenteral fluids should be carefully controlled in order to avoid overloading the circulation and precipitating acute circulatory failure and pulmonary edema

Some Special Histopathological and Clinical Features

Some histopathological and clinical features of cardiac and/or vascular involvement are observed in boutonneuse fever, rickettsialpox, Q fever, and trench fever.

Boutonneuse Fever

Boutonneuse fever (Marseille fever), a tick-borne, acute rickettsial disease endemic in the Mediterranean basin, is characterized by an abrupt onset, fever lasting eight to 14 days, pains in the back and the limbs, headache, insomnia, a rash, and an almost always favorable outcome. The case fatality is less than one per cent The site of the infecting bite can be demonstrated in 80 per cent of cases The initial lesion is a small ulcer showing a black necrotic center (*tache noire*) This ulcer shrinks, dries to form a black eschar Boutonneuse fever without primary eschar presents a picture very similar to murine typhus. In both there is a maculopapular eruption, although in boutonneuse fever the papular tendency is more pronounced (Woodward). Boutonneuse fever may occasionally produce a hemorrhagic rash, the lesions are profuse and scattered over the palms, soles, and face and persist longer leaving pigmented marks

A positive Weil-Felix reaction occurs late in the course of the illness. Histologic sections of the maculopapular rash revealed hyperplasia of vascular endothelium, lymphocytic and monocytic perivascular infiltrations affecting the papillary and subpapillary vascular plexus. Acute congestion and hemorrhages occur.

In one of our cases, the 50 year old patient complained of headache, palpitations, breathlessness on exertion. There was tachycardia, profuse sweating. Electrocardiographic alterations were minimal (PR prolongation 0 23"). Finally, the patient recovered without sequelae.

Aureomycin has been found to shorten the period of disability. The boutonneuse fever of the Mediterranean area is closely related to the boutonneuse fever of Equatorial Africa, and there is cross-immunity between the two types

Rickettsialpox

Rickettsialpox is a mite-borne, acute disease characterized by an initial lesion, fever lasting for one week, a varicelliform maculopapular rash Headache, chills, or chilly sensations characterize the onset of systemic involvement Occasionally enlargement of the spleen and of lymph nodes and tachycardia occur The initial lesion may persist for three weeks and longer The picture may be confusing especially in the rare cases with absence of the initial lesion Rickettsialpox shows similarities to boutonneuse fever, but there are some clinical and serological differences, especially the failure of convalescent serums to agglutinate Proteus X 19 The patients show a high antibody titer during convalescence.

Histopathology of the cutaneous lesions show vasculitis. Some of the capillaries undergo a thrombotic process Dolgopol reported extensive histologic alterations in a case of rickettsialpox. In a fresh papulovesicular lesion, the vesicle occupied the entire thickness of the epidermis, the intraepidermal vesicle covered with a thick layer of epithelium showed hydropic changes and some disintegration of cells with fragmentation of nuclei The basal layer was largely preserved. Nuclei of polymorphonuclear leucocytes migrating toward the vesicle were present in the upper layer of the corium, there was also a thrombosed blood vessel Slight diffuse mononuclear infiltration was observed in lower layers of the corium The maculopapular rash of rickettsialpox is microscopically similar to the eruptions of other rickettsial diseases in regard to character and distribution of the cellular infiltrates, but the infiltrates are much

heavier than in other rickettsial diseases. Karyorrhexis is quite prominent. Mast cells densely packed with metachromic granules are numerous, while plasma cells are absent. The vascular changes resemble those of scrub typhus but are less severe. Incomplete homogenous thrombi and absence of arteritis and hemorrhages are typical of the eruption of both diseases.

According to Dolgopol, microscopic examination of the rash has its place as an aid in the diagnosis of rickettsialpox, especially if a suspicious disease appears in an area previously free from that disease. The histologic examination of a skin lesion may be completed long before the report on the second specimen of blood (for complement fixation test) is available, and cultivation of the rickettsia from the blood of the patients is so complicated and protracted as to make it unsuitable for practical diagnostic purposes.

Rickettsialpox has to be added to the other rickettsial diseases in which the effect of Aureomycin is curative.

Q Fever

Q fever is usually characterized by an extremely sudden onset, chilliness, fever, severe headache, anorexia, muscular pains, and later respiratory and gastrointestinal symptoms. It is endemic in many parts of the world and a widespread infection of man and domestic animals Q fever is caused by *Rickettsia burneti* which possesses the general properties of other rickettsiae, i.e, their morphology, staining properties, and growth requirements; it differs from them in its relative resistance to adverse conditions of temperature and humidity and to chemical agents. Q fever does not develop agglutinins against proteus organisms *Rickettsia burneti* is easily isolated from the blood of patients by inoculation of guinea pigs during the first day of illness

The most significant finding in Q fever is an unproductive cough and crepitant rales in the chest in the majority of cases, occasionally there is slight dullness, diminution of breath sounds, or a friction rub, frequently in the lower lobes. Radiological evidence of multiple pulmonary infiltration is common The multiplicity of lesions scattered through the lung is said to be one of the distinctive features of Q fever. In other cases, there is an infiltration of uniform ground glass density, circumscribed in peripheral portions of the lung But generally the pneumonia is clinically indistinguishable from atypical pneumonia of the cold agglutinin type, influenza pneumonia, or psittacosis

Q fever lasts from one to 15 days or more. The pulse is slow in relation to the height of fever. Severe cases may show a slight cyanosis. Hepatomegaly and liver tenderness are frequent, while splenomegaly is an occasional finding. Pleural effusion may occur. Q fever often causes a mild influenza-like disease without any localization in the lungs.

Q fever does usually not develop a cutaneous rash, but exceptionally there may be a maculopapular eruption (Denlinger; Beck, Bell, Shaw, and Huebner; Simrock and Siegert; Babardieri). Q fever may resemble the course of brucellosis. Involvement of the central nervous system and of the meninges is frequent, but aseptic lymphocytic meningitis as the only sign of Q fever is rare (Denlinger; Wegmann; Siegert; Germer and Schauber).

It is rarely a serious disease and is usually susceptible to antibiotics. But there are Q fever patients who continue to have an evening rise in temperature for more than two months. A recurrence of symptoms, fever, and even consolidation may occur in some cases. Complications may develop in the second to the sixth week after the onset of Q fever, even when the fever is apparently controlled by Aureomycin or a similar antibiotic. Such complications include thrombophlebitis, pulmonary embolism, epididymitis, encephalitis, pancreatitis, lymphocytic meningitis (Moeschlin and Koszewski) Complications occur especially in persons over 40 years of age. These patients are weak, easily fatigued, somewhat mentally depressed for long periods after fever has subsided. A more prolonged Q fever has been observed also in elderly patients. Marmion, Stocker, McCoy, Malloch, and Moore reported four fatal cases of Q fever; two (possibly three) of them had pulmonary infarction. One of them had been febrile intermittently for three months when he died, and another had had attacks of fever for several years and had a high titer of Q fever antibody for at least the last six months of life. These cases suggest that Q fever may become chronic, and although the disease usually responds to antibiotics such as Aureomycin, Chloromycetin, and Terramycin, the severe long standing cases are resistant to drugs.

Varying degrees of invasiveness of Q fever may explain an unusual intensity of infection depending at least as much on the susceptibility of individuals as on any property of the virus. *Rickettsia burneti* may continue to parasitize not only a guinea pig but also a human host for many years after the initial invasion.

Few details of pathology of Q fever are available. Q fever is clinically

and pathologically much more variable than other rickettsial diseases. The principal finding is a focal or confluent bronchopneumonia and edema of the lung. The bronchopneumonia with mononuclear cells predominating in the exudate is consistent in type with a rickettsial infection (Perrin). According to Wolbach, the long persistence of x-ray evidence of consolidation suggests that resolution is not the usual manner of repair and that organization of the exudate is the usual course in recovery. This pathology may explain that in older individuals Q fever may be much more serious especially in cases where fever persists for several months. Cardiovascular involvement in Q fever is not conspicuous. A relative bradycardia is regarded as characteristic of the disease in nearly all the outbreaks. Denlinger found in some patients functional systolic murmurs of grade 1 or 2 intensity, heard best at the apex. A pericardial rub was heard in one patient over a seven day period starting with the third day of illness. This patient had pneumonia in the lingular portion of the left upper lobe. Perrin found in a 43 year old man having died from Q fever coronary arteriosclerosis with an old organized myocardial infarction which may have probably exerted an unfavorable influence on the course of the disease. But there is no evidence that persons not otherwise suffering from heart diseases experience demonstrable embarrassment of cardiac function during an acute attack of Q fever. But the occasional possibility of cardiovascular involvement in Q fever is suggested by some findings in experimental animals Lillie found in guinea pigs infected with *Rickettsia burneti* small focal granulomatous lesions scattered throughout practically all organs and tissues consisting of vascular endotheliosis and perivascular collections of cells of the lymphocytic series, monocytes and fibroblasts. Germer did not observe disseminated vasculitis or perivasculitis but interstitial myocarditis Interstitial myocarditis, found in infected guinea pigs, is similarly comparable with that described in human infections (infectious mononucleosis, mumps, poliomyelitis) (Germer).

Q fever is very resistant to sulfonamides and penicillin Many physicians consider Aureomycin to be superior to any previous therapy used for this disease though the response of Aureomycin is variable

Transfusions and oxygen therapy are occasionally necessary in supportive treatment of severe cases Patients convalescing from Q fever should not be allowed to get up or to leave the hospital too soon and should not be permitted to return to work until the temperature has been normal for three to four weeks (Moeschlin and Koszewski).

Trench Fever

Trench fever (Quintana fever, Five day's fever, Shin bone fever, Wolhynian fever, His-Werner Disease) is an infectious disease characterized by sudden febrile onset, postorbital headache, pains in the limbs, especially in the shins, frequent enlargement of the spleen, and not rarely by a pale, blotchy rash Characteristic is a tendency to new attacks occurring weeks, months and sometimes years after the primary onset.

The disease was prevalent from 1915 to 1918 during World War I on the Eastern and Western fronts, probably originating in endemic focuses in Russia. It appeared on the Western front "wholly unexpectedly, like a bolt from the blue." Following demobilization, the disease disappeared, but it retained the potentiality of again becoming epidemic when similar conditions of lousiness and overcrowding had again occurred. This was the case in World War II in the German Forces on the Eastern and Southern fronts. It did not occur on Allied sides

Trench fever seemed to be limited to Central Europe It was rarely observed in the civil population. But from other parts of the world trench fever has been also reported, it was present in Spain, in Abyssinia, in Japan. Parrot described a case from Algeria which conformed in all its clinical features to trench fever This author suggested that some of the cases diagnosed in Algeria as relapsing fever without spirochetes may be examples of trench fever

The disease is usually conveyed by the bite of the louse. The agent of the disease is present in the blood of these patients and occasionally of healthy persons Experimental transfer of the infection from man to man was effected by intravenous inoculation of infected blood. Infection was also achieved by bringing the causative agent present in crushed lice in contact with the abraded skin of a non-immune person. The presence of *Rickettsia quintana* or *wolhynica* in the intestines and feces of lice is correlated with the infectivity of the disease

Strains of lice free of *Rickettsia quintana* may become infected with this organism when fed upon patients with trench fever not only in the acute stage but even many months after the first attack of the disease. According to Weyer, the xenodiagnosis of feeding body lice on persons was successful with a considerable number of patients

Some species of the *Rickettsia quintana*, isolated from patients, have kept in the laboratory in continuous lice passages Explantation-experiments with infected stomachs of lice showed that even a fortnight after the

explantation the Rickettsia could be inoculated to lice by vaccinating them with culture-emulsions. Dried stomachs of infected lice transmitted by rectal vaccination to body-lice after 219 days and dried feces of infected lice transmitted after two and one half years offered positive results.

Mohr and Weyer reported positive louse feeding tests of patients who suffered from trench fever 1370, 1010, and 2880 days after onset of illness. Kostrzewski described positive results after five to eight years after the first attack. Hoenig and Mohr reported a case of trench fever in which the Rickettsia were detected in a person by the louse feeding test ten years after the presumably first attack and three and one half years after his departure from a region in which reinfection was possible. There was a history of many illnesses suggestive of recrudescences of the disease after the onset.

The Rickettsiae of trench fever are capable of survival in the human body for many years after the beginning of the disease; symptomless or unrecognized attacks are frequent and maintain the chain of infections.

The louse feeding test has also demonstrated that persons who show no symptoms of trench fever may occasionally harbor Rickettsias.

The Rickettsiae which are regarded as apathogen are considered as identical with *Rickettsia quintana*. Kostrzewski thought that such apathogen Rickettsiae may demonstrate their pathogenicity when they reach a susceptible host. The *Rickettsia quintana* is present extracellularly along the cuticular border of the intestinal lining of the gut of the louse, thus differing from other pathogenic Rickettsias

There are also certain morphologic pecularities in *Rickettsia quintana*. Useful serologic tests have not been developed in trench fever No small laboratory animal is susceptible to *Rickettsia quintana* Attempts at cultivation of *Rickettsia quintana* in the chick embryo and in tissue cultures have failed Arthropods in which growth and survival occur are all kinds of human lice and some ticks (Weyer)

Jungmann was the first who successfully inoculated a monkey Codeleoncini reported the inoculation of two baboons with positive results. Mooser and Weyer inoculated seven Rhesus monkeys with four strains of *Rickettsia quintana* and all animals showed a Rickettsemia lasting ten to 82 days as proven by louse test

The incubation period of trench fever in man is from ten to 30 days with extreme limits from five to 60 days Prodromal symptoms of headache and general malaise during the incubation period may or may not be

present. The onset is acute with shivering and a rise in temperature to 102 or 103 F. Severe headache, anorexia, giddiness, are almost constant at this stage Nausea, vomiting, constipation or diarrhea may occur. Laryngitis and bronchitis may be present but are not severe. The characteristic symptoms of trench fever are the pains over the long bones, especially in the shins The pain felt in the shin bones are lancinating or boring, worse at night. Pains in the legs are not present in all cases Alternate shivering and sweating are features of the disease. Occasionally the onset was insidious and symptoms of fever, pains in the limbs, headache, giddiness, and tachycardia have called attention to a more chronic form of trench fever.

On examination, the patient's face was flushed, the skin was moist; there was a mild degree of conjunctival congestion (pink eye). The shin bones were very tender and the skin over them hyperaesthetic. Spots may appear on the second or third day or during relapse, they are pink in color and extend over chest, back, and abdomen. There were several types of fever. Characteristic was a paroxysmal spiky fever, the temperature suddenly shooting up to 102 or 103F. lasting 24 to 30 hours and recurring after five or seven days apyrexial interval. This type of a certain periodicity of the fever may last several weeks or months. Another type was a prolonged undulant fever lasting for six or seven weeks with slight remissions. According to Byam et al, too much reliance should not be placed on the type of the temperature curve when making a diagnosis of trench fever. Some cases may be afebrile throughout.

In all cases, the pulse rate usually was about 100 or more during the fever but may be higher in relapses An increase in pulse preceded relapses and may also be the only evidence of a relapse.

The spleen was frequently enlarged during the fever period and thereafter. White blood cell counts varied from 4000 to 30,000 per cu. mm. In the urine, a trace of albumin was sometimes present. Hemorrhagic nephritis was an exceptional occurrence. Encephalomyelitis and neuritis were important findings of the disease, but involvement of the autonomous nervous system was more frequent. A pleocytosis and increased protein has been found in the cerebrospinal fluid. According to Mohr and Hirte, the invasion of the central nervous system in trench fever may be produced by the *Rickettsia quintana* which is endowed with marked neurotropism. Aschenbrenner pointed out that allergic mechanisms play a role in the causation of the encephalomyelitis of trench fever.

Other complications were myocarditis, anemia, and exhaustion. Tachycardia was a frequent occurrence. The area of cardiac dullness was sometimes increased in width in chronic cases. Occasionally, the picture resembled paroxysmal tachycardia. According to Byam et al, a number of patients revealed cardiac irregularities only during the exacerbations of the disease. Breathlessness on exertion, precordial pain, and giddiness are features of subacute and chronic forms of trench fever.

Generally these symptoms have not been attributed to direct heart involvement, but slight myocardial damage could not be excluded (Schittenhelm, Dennig). Aschenbrenner thinks that a long lasting postinfectious tachycardia in trench fever is caused by autonomous imbalance.

According to Mohr and Hirte, cardiovascular disturbances in trench fever are transient and harmless. In 43 cases of Mohr and Hirte, there were only two cases with flattening of T waves and depression of ST segments, perhaps produced by precedent diseases

It is probable that in a greater part of cases cardiovascular symptoms may be caused by neurocirculatory asthenia as sequelae to an exhausting disease, but the peripheral circulation may be also primarily affected in this disease. It is understandable that quick rehabilitation of many patients was difficult, finally all of them recovered after a period adequate for convalescence.

We don't know much on the pathologic histology of trench fever. Biopsy of cutaneous lesions show that the corium of the spots of trench fever is hyperemic and edematous There is perivascular lymphocytic infiltration with a variable number of polymorphonuclear leucocytes.

The skin lesions differ from those seen in epidemic typhus in that in trench fever there are no necroses of the endothelial cells of the vessels and no hyaline thromboses. At necropsy, interstitial myocarditis has been found in two fatal cases of trench fever (Dorr, Reuter) But in these cases there has been typhus fever some months prior to trench fever. Interstitial myocarditis may have been caused by typhus in these cases In another fatal case, there was no heart involvement (Aschenbrenner). These fatal cases were not caused by trench fever. Apart from one suicidal case, the two other persons died suddenly following the administration of Prontosil and Pyrifer.

Trench fever itself has no mortality Recovery was often delayed in aged and debilitated persons. Treatment was symptomatic Sulfonamides, quinine, and other remedies failed.

The discovery of Aureomycin marks the beginning of domination of trench fever Mohr and Hirte, Hoenig, and Weyer advocated use of Aureomycin in the treatment of trench fever, stressing the remarkable therapeutic effect in two cases. The treatment with this antibiotic must now be considered whenever the diagnosis appears reasonably certain. Early treatment is important for the prevention of cardiovascular and other complications of trench fever.

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Addendum

After this monograph had been completed (July, 1955) it became evident that a number of older studies had been overlooked and new valuable contributions had been published in the meantime.

Hence, this addendum was prepared in order to give the reader a brief account of some additional studies and recent advances. (References are to Chapters and Sections in the main text.)

Chapter II

Saphir and Field investigated the complications of isolated myocarditis in children. The fact that multiple emboli are often present in several organs indicates that the heart is the source of these emboli The cause of the emboli is obviously the inflammatory change close to the endocardium which produces subendocardial edema or even localized foci of mural endocarditis, predisposing to the formation of thrombi. Multiple emboli constitute a serious complication and may contribute to death.

According to de la Chapelle and Kossmann, cardiac catastrophes will be avoided if the physician considers the possibility of myocarditis in the course of all types of infectious diseases It would seem the part of wisdom to give all patients with myocarditis occurring in various infectious diseases sufficient rest in bed to permit the myocardial inflammatory process to pass into a healed stage as determined clinically and electrocardiographically

Sokoloff gave a brief review of the capillary syndrome in viral infections. Involvement of the capillary system is much more frequent and common in these diseases than has generally been appreciated It is possible that the damage to the capillary wall is one of the contributing factors to the generalization of viral infection Citrus flavonoids, otherwise known as vitamin Q or the capillary-permeability factor, should decrease the injury to the capillary wall induced by viral infection

Although recently some experimental evidence of storage of Periston has been reported, it must be emphasized that plasma substitutes have their main action by virtue of the colloidal osmotic pressure which they exert.

The mechanism of this pressor effect is not understood, but in the case of polyvinylpyrrolidone it has been suggested that a reversible combina-

tion with plasma globulins and globulins in the cell wall reduces the capillary permeability in addition to exerting a colloidal osmotic pressure effect (Fairlie).

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Chapter III

Section 1. Measles

Further information continues to develop concerning electrocardiographic changes in measles. Bengtsson and Berglund examined 451 cases of measles electrocardiographically (409 children and 42 adults). Abnormal electrocardiographic findings were observed in 2 of the children (less than 0.5 per cent) and 7 adults (16.7 per cent). The changes were transient and lasted, on an average, 2 to 3 weeks. One two year old child developed a right bundle branch block which was still present one year later.

Goldfield, Boyer and Weinstein made a total of 359 electrocardiograms of 106 cases of measles (an average of 3.7 per patient). In 48 instances the infection was uncomplicated. Pneumonia was present in 28, 5 developed otitis media, encephalitis occurred in 16, and 9 suffered from miscellaneous concurrent diseases. Twenty (19 per cent) were considered to have definite electrocardiographic abnormalities, while five (4.7 per cent) were considered borderline and, therefore, were not included in the statistical analysis. With one exception, the abnormalities were limited to changes in the T waves or the P-R interval. The exception was a child with measles who developed numerous auricular premature beats, beginning 16 days after admission and persisting for one week. Two patients with right bundle block were encountered. In the first case this abnormality was not attributed to measles, and in the second the aberrant conduction was considered a result of tachycardia and not to be associated with measles per se. Abnormal tracings appeared as early as two or, at the most, 20 days after the onset of the rash, and usually reverted to normal within a week. It is tempting to speculate that though anatomic involvement of the heart does occur in measles, it is rarely, if ever, severe enough to be clinically detectable.

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Section 4. Varicella

In a recent report Hampton, Jr. described the case of a woman, 25 years old, suffering from primary varicella pneumonia. She presented a typical chickenpox rash, dyspnea, tachypnea, cyanosis, hemoptysis and prostration when she was admitted to the hospital. The lower two-thirds of the chest were filled with medium, sticky rales. Chest x-ray films revealed an extensive, diffuse nodular infiltration on both sides. The heart showed sinus tachycardia and a Grade 2 apical systolic murmur. Total proteins were 5.9 Gm. per cent and the albumin-globulin ratio was 1.1:1. The poor arterial oxygenation was illustrated by an arterial oxygen saturation of 85.5 per cent on the sixth day of pulmonary involvement. The course was that of slow resolution of the pneumonia.

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Supplement 1

Erythema infectiosum (Fifth disease, megalerythema epidemicum, exanthema variegatum, erythema simplex marginale).

Erythema infectiosum is a rare, probably viral disease It is mildly contagious and minor epidemics have been encountered It is a disease of children and young adults, with an incubation period of 6 to 14 days. It is characterized by sudden onset and a polymorphous rash on the cheeks, arms and legs, chiefly on the extensor surfaces, and, to a lesser degree, on the trunk. The exanthema begins as a flush over the cheeks, gradually growing into a bright erythema with raised edges and spreading to produce a butterfly configuration. In our cases the rash was most evident on the face. Within 2 to 4 days the eruption may appear on the extremities —to a lesser extent on the chest—as discrete macula, which later grow into papules and coalesce into a lace- or garland-like pattern. The rash fades within 3 to 21 days without desquamation There is no enanthema. Sore throat, rhinitis, malaise, slight enlargement of lymph nodes and eosinophilia (5 to 15 per cent) may be present. Petechial hemorrhages on the palate, hemorrhagic nephritis and hemorrhages into the skin may

occur and are a sign of vascular damage. Evidence of liver damage could also occasionally be found.

Hoffmann described, on the basis of skin biopsies, perivascular round cell infiltration of the suprapapillar veins and capillaries and edema of deeper epidermal layers.

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Supplement 2

Roseola infantum (Sixth disease, exanthema subitum, rose rash of infancy).

Roseola infantum is a viral disease, the infection being the most common febrile exanthema in infants. The disease chiefly attacks during the first three years of life, with peak frequency during the second half of the first year. Older children and adults are not frequently affected, but some adult cases have been described (Zahorsky, Greenthal, Cutts, James and Freier). According to Pick and Sparling, practically all affected infants receive their infection from adult carriers.

Roseola infantum is contagious and may occur in limited outbreaks or epidemic form, especially in institutions and hospitals.

The incubation period is from 5 to 15 days. The disease is characterized by an abrupt onset, three or four days of high fever, suggesting influenza, followed by sudden appearance of a rash (resembling measles or German measles) persisting for 1 to 3 days. For diagnosis it is essential that the rash appears as the temperature falls to normal. The rash occurs on the trunk and, to a lesser extent, on the face and limbs. There are mild or rudimentary forms of fever for 1 or 2 days, and a slight rash lasting a few hours. Severe cases with high and prolonged fever also occur. The disease is frequently associated with convulsions, which may last several minutes or hours. Convulsions occur either at the onset of roseola infantum or on the second or third day. There may be only one convulsion during the course of the disease or repeated convulsions on the same or successive days (Windorfer). The convulsions are probably provoked by meningo-encephalitic processes. This view is supported by observations of transient or persistent pareses subsequent to convulsions. Vomiting, diarrhea, meningism, and tension of the fontanel are observed. *Pharyngitis*, tonsil-

litis, bronchitis, dyspepsia and otitis may occur, the latter most frequently. The cerebrospinal fluid is clear, and the number of cells and sugar content may be increased.

Leukopenia is observed as early as the febrile stage and later becomes pronounced. The spleen is sometimes palpable and lymph nodes may be palpably enlarged. Recurrences are rare.

The disease should not be considered as absolutely benign. Berenberg, Wright, and Janeway speculated, as did Windorfer, that some cases of sudden death in infancy may be caused by severe, unrecognized roseola infantum. A disease in which meningoencephalitis may occur must be regarded as potentially severe despite a usually favorable prognosis. Berenberg, Wright and Janeway reported on a 10 month old infant who had all the symptoms of roseola infantum, including a typical rash. He became critically ill on the second day of the disease and went into a shock-like state of collapse with rapid, thready pulse, dyspnea, cyanosis and cold, mottled skin This did not appear to be due to hyperpyrexia. For a few hours it appeared unlikely that he would survive, although he eventually responded to symptomatic shock therapy The pathogenic agent shows neurotropism and dermatropism, since these symptoms predominate. The agent is experimentally transmissible to humans and monkeys. An indirect transmission may also occur The viral etiology of roseola infantum appears to be established (Neva and Enders), and the clinical picture of the disease resembles the West-Nile virus infection as described by Bernkopf, Levine and Nerson. The main symptoms of West-Nile infections are fever for 2 to 3 days and a subsequent macular or papular rash. Other symptoms observed are leukopenia with a relative lymphocytosis, headache, occasionally pain in the back and the limbs, abdominal pain, diarrhea, and vomiting Brudzinski's sign is present in children. Most of the cases occur in infants under the age of two and in children from three to five years The differential diagnostic significance of the West-Nile virus infection is evident in areas in which West-Nile virus is present, i e., in Africa and the Near East

The features of an "unusual epidemic exanthema" (as occurred in Boston in 1951), a febrile illness of short duration, are similar to those of roseola infantum (Neva, Feemster, and Gorbach) The ages of 18 patients ranged from 4 months to 26 years. The maculopapular rash appeared in most cases after the onset of other symptoms or signs, and within one or two days after fever had subsided In a few cases the eruption

developed in the absence of other previous symptoms or during the fever. In two adult patients the early stage of the illness was associated with frank shaking chills. There was no cardiovascular or central nervous system involvement. A group of new transferrable agents was isolated from the feces of several patients by tissue-culture method and the development of neutralizing antibodies associated with the illness was demonstrated. Both of these suggested the etiologic relationship of these new agents to the disease.

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CHAPTER V

Section 1 Influenza

Dr White's experience with heart involvement in influenza changed between the third and fourth editions of his book *Heart Disease*. He stated (1951) that "cardiac injury in influenza had long been suspected, and by some incriminated, but only in the last few years has actual proof been presented. It is quite possible that lesser lesions of the heart muscle have often resulted from influenza, but serious or fatal myocarditis is rare. Most of the symptoms, which years ago were attributed to such a condition, were characteristically those of a fatigued state or neurocirculatory asthenia which so often complicates the convalescence from any infection."

According to Bieling, the most developed stage of the influenza virus in the infected human body may either coincide or somewhat precede the abrupt onset of the disease. The physician who examines a typical influenza case sees a stage of the disease in which toxic effects on the vascular system and morphologic alterations directly produced by the

influenza virus have already occurred. The great importance of clinical recognition of acute hypovolemia in influenza infection has become increasingly evident. Schunk, Kluetsch and Schaudig investigated plasma and blood volume, hematocrit, circulation time, venous pressure and arterial blood pressure during and, when possible, after influenza. They found there was an acute hypovolemia in the febrile stage, although this hypovolemia may not be present in the convalescent stage. Hypovolemia in influenza is produced by capillary damage which may lead to functional vascular disorders, shock and collapse. The administration of sympathol, cardiazol and veritol in cases of severe influenza is recommended. In cases associated with collapse or shock syndrome, the importance of plasma or plasma substitutes (Periston N, Macrodex [dextran]) and noradrenalin is stressed.

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Section 3. Interstitial Pneumonia in Infants

Weisse considered interstitial plasmacellular pneumonia, which occurs between the eighth and tenth week of life, as a pneumonia caused by a pneumotropic virus. Weisse and Bieling were able to produce identical pulmonary alterations in mice and guinea pigs by inoculation of bacteria-free material from affected infants.

Gruenwald and Jacobi described mononuclear and interstitial pneumonia which inflicted children with sudden or rapid death. A viral etiology was suggested, but no evidence of this was available.

Deamer and Zollinger stated that an unusual type of infantile plasmacellular pneumonia frequently occurred in certain European countries. The disease is almost clinically asymptomatic until late in its course, and shows a marked predilection for premature or immature infants. It is confined to the age period of six weeks to four months. The diffuse interstitial pulmonary infiltration is caused by mononuclear cells which closely resemble plasma cells. An alveolar exudate is also present. About 22 per cent of patients die of clinically recognizable asphyxia. This disease has all earmarks of an infectious process and is probably of viral origin.

Benecke, Asteroth, Gloggengiesser, Ammich and Weisse observed dilatation of the heart, and particularly of the right half of the heart, in

infants dying of interstitial plasmacellular pneumonia. Weisse saw transient sinus tachycardia and other electrocardiographic alterations (especially right cardiac strain) in non-fatal cases of plasmacellular virus pneumonia in infancy. Weisse also described a case of interstitial plasmacellular pneumonia associated with encephalitis and slight meningitis. Pneumocystis carinii was found in the lungs. Generalized cytomegalic inclusion body diseases with acidophilic intranuclear inclusion bodies in the brain and lungs were also observed. Fingerland and Vortel described cases of interstitial plasmacellular pneumonia in which, according to Weisse, cytomegalic cells with nuclear inclusion bodies were present in the submaxillary salivary glands. The association of interstitial plasmacellular pneumonia, Pneumocystis carinii, in the air passages and cytomegalic inclusion bodies in the salivary glands was reported by Baar.

Raspe, Loehr, Henning and Terbrueggen emphasized the importance of increased capillary permeability in interstitial plasmacellular pneumonia of premature infants. Henning and Terbrueggen assumed diminution of plasma proteins to be a major factor causing the development of disturbances. According to Weisse, conspicuous changes in plasma proteins in interstitial plasmacellular pneumonia were not evident, but "physiologically very low" values of total proteins were usually found in premature babies.

Lunseth, Kirmse, Prezyna and Gerth stressed that the histologic pattern of plasmacellular pneumonia bore a marked resemblance to that of the early state of acute interstitial fibrosis of the lungs (the Hamman-Rich syndrome). The chief difference appears to be that in the latter the interstitial inflammatory infiltrate consists of histiocytes, and only a few, if any, plasma cells. Also, the end stage of the latter is marked by considerably more fibrosis; this may be because it runs a longer course than plasma-cell pneumonia. There is even considerable resemblance between the clinical course of the two diseases. In both the Hamman-Rich syndrome and plasma-cell pneumonia there is frequently a long, relatively asymptomatic period preceding a rather rapidly fatal course; and, at necropsy, there is the same paradox of finding a chronic process in the lungs. The authors conclude that "it is tempting to consider the possibility of a close relationship between the two diseases."

Weisse emphasized the importance of new investigations on the significance of the regular findings concerning: (1) Pneumocystis carinii for the development of interstitial plasmacellular pneumonia, (2) the relation-

ship between cytomegalic inclusion body disease and interstitial plasmacellular pneumonia, (3) the position of giant cell pneumonia, and (4) the conception of interstitial plasmacellular pneumonia as the primary atypical pneumonia of a certain age group.

There still remains the question of whether or not all the discussed pictures of diseases are different illnesses occurring with a certain frequency and clinical course in certain age groups.

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Chapter VII

Section 1. Viral Encephalitides and Encephalomyocarditis

In the discussion at the Second International Poliomyelitis Conference (Copenhagen, 1951) Van Creveld mentioned a virus infection which probably should be considered in the differential diagnosis of the nonparalytic forms of poliomyelitis The author observed a case of "encephalohepatomyocarditis" in a 4 month old[1] infant, and assumed a viral etiology of the disease because of identical observations in animal experiments and the demonstration of intranuclear inclusion bodies in the heart and liver.

Studies during the last years have indicated that tick encephalitis is frequently associated with transient myocardial impairment. Hloucal and Slonim observed 40 cases of tick encephalitis which occurred in the neighborhood of Strakowice, Czechoslovakia. In five cases transient electrocardiographic alterations suggestive of myocardial damage were present. Thirteen positive results of complement fixation tests with sera

from 24 of 30 patients were reported. Lasch and Moritz observed in 1948 near Villach in the province of Styria, Austria, cases of recurring meningitis with recovery after a prolonged course of many weeks, and an epidemic outbreak of meningo-encephalomyelitis in 1953. The number of cases was: 62 in 1948, 29 in 1949, 15 in 1950, 34 in 1951, 19 in 1952, and 64 in 1953.

Many of these patients had been bitten by ticks, while others may possibly have been bitten. The castor bean tick (Ixodes ricinus) is believed to have transmitted the virus in the cases of Lasch and Moritz, Hloucal (1953), and Hloucal and Slonim (1954). Lasch and Moritz demonstrated the ability of patients' serum to fix complements with the antigen prepared from a strain isolated from patients with the same disease who lived near the Austrian border in the Slovenian province of Yugoslavia. The virus which caused the disease belonged to the same group of viruses as the louping-ill virus and the viruses isolated from outbreaks of human tick encephalitis in Czechoslovakia and Russia. Symptoms of patients suffering from this disease were an enlargement of the spleen and, occasionally, an enlarged liver. There were also bradycardiac and electrocardiographic changes suggestive of transient myocardial impairment. Electrophoresis of the serum of patients showed reduction of albumin and an increase of alpha-, beta-, and gamma-globulin. Ophthalmologic examination revealed papillitis in 50 per cent of the patients. Signs of focal nephritis and of hepatorenal syndrome were also observed. Recovery occurred in all patients

Clarke, Bayliss and Cooper reported three cases of Landry-Guillain-Barré syndrome which became complicated by an acute circulatory failure, and was fatal in one patient Evidence was presented to suggest that in some cases involvement of the myocardium, rather than loss of peripheral tone, may have been the cause of circulatory collapse. Klein described a fatal case of infectious mononucleosis associated with Landry-Guillain-Barré syndrome and interstitial myocarditis. Electrocardiographic evidence of myocardial impairment was obtained five days prior to death Reske-Nielsen and Mogensen observed a fatal case of a 19-year old youth inflicted with infectious mononucleosis and polyradiculitis. Histologic examination revealed infiltration of mononuclear cells into the heart muscle and many organs It has been suggested that the multiplicity of nervous symptoms in infectious mononucleosis may have an allergic origin, for there is no known viral infection, apart possibly from poliomyelitis, which produces such capricious involvement at every level of the nervous system. In other words, the basic pathology of the nervous

ship between cytomegalic inclusion body disease and interstitial plasmacellular pneumonia, (3) the position of giant cell pneumonia, and (4) the conception of interstitial plasmacellular pneumonia as the primary atypical pneumonia of a certain age group.

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Chapter VIII

Coxsackie Virus Disease

Locke and Farnsworth, Finn, Weller and Morgan reported pericarditis as a complication of epidemic pleurodynia. van Creveld, de Groot, Hartog and Lie Sing Kim stated that in cases of Bornholm's disease a myocarditis was occasionally found which resembled the histiologic picture of acute interstitial myocarditis of infancy.

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Chapter IX

Supplement 1.

Rift Valley Fever

Rift Valley fever (enzootic hepatitis) is primarily a disease of cattle and sheep. Infection of human beings is an accidental event in the natural history of the disease. In humans Rift Valley fever is clinically undistinguishable from sandfly fever, dengue fever and influenza. The mortality is very low The disease has been reported from Africa. Daubney and Hudson (1931) first described an enzootic hepatitis affecting sheep, cattle and goats in the Rift Valley of Kenya Colony (British East Africa). Infections among persons in contact with infected animals then occurred, and the paper by these authors includes a report of Garnham relating to a successful experimental transmission to man.

Rift Valley fever is caused by a very small virus, and has a mortality of more than 95 per cent among unborn and newborn lambs and a moderate mortality in ewes and cows. In sheep the illness shows extensive focal necrosis of the liver, surrounded by pin-point hemorrhages, toxic degeneration of the spleen and lymph nodes, petechial hemorrhages in all viscera, hemorrhagic enteritis, tubular nephritis, and subepicardial ecchymoses on the ventricles of the heart. There are also subendocardial extravasations in the left ventricle and hemorrhages in the cortex of mesenteric lymph glands. The liver shows hyaline degeneration closely resembling the Councilman bodies seen in the human liver infected with yellow-fever

complications, or even of the disease itself, may be primarily a disorder of the blood vessels, i.e., an allergic vasculitis (Librach).

Bernstein and Wolff deprecate the theory that the neurologic complications in infectious mononucleosis may have such a basis. They state, "it appears that the nervous system is directly invaded by the unknown agent causing infectious mononucleosis."

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Section 2. Poliomyelitis

Uflacker found, among five fatal cases of poliomyelitis in children, two with interstitial myocarditis. He also found that 21 of 62 poliomyelitic cases revealed abnormal electrocardiograms, and of these 21 cases, 20 showed changes of one or more T waves and 7 indicated Q-T prolongations. The electrocardiographic changes, suggestive of myocarditis, appeared early in the course of the disease, and persisted for several weeks or months. The prognosis of myocarditis in poliomyelitis is usually good, but the heart disease may present a danger for patients suffering from bulbar and bulbospinal forms.

In these patients respiratory embarrassment may occur simultaneously with circulatory failure which, in turn, is due to destruction of the vasomotor center. If the heart muscle is already damaged at this time, anoxemia and circulatory collapse may result in sudden myocardial failure. Schaper and Schultze-Jena report abnormal electrocardiographic findings in 28 of 54 poliomyelitic children (51.9 per cent). Cardial or extracardial causes were responsible for these alterations. Interstitial myocarditis was observed in three of four fatal cases.

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Chapter X

Section 2. Infectious Mononucleosis

Klein who reported a fatal case of Landry-Guillain-Barré syndrome in infectious mononucleosis, found cellular infiltrations of large round cells with basophilic plasma situated between myocardial fibers. There is a moderate proliferation of the interstitial tissue. The alterations observed in the heart were compatible with electrocardiographic evidence of myocardial damage seen five days prior to death. Werner observed in a fatal case of infectious mononucleosis that one myocardial perivascular focus consisted of lymphocytes. Reske-Nielsen and Mogensen reported mononuclear cell infiltration of the heart in a fatal case of infectious mononucleosis and polyradiculitis.

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Chapter XI

Epidemic Typhus

Brinkmann stressed the importance of myocarditis in epidemic typhus. Myocardial lesions of focal shape, so called "typhus nodules", and diffuse interstitial myocarditis were present. The myocarditis which occurs underneath the endocardium may be responsible for involvement of the conduction system and sudden death. Cardiovascular disturbances have been observed 1 to 2 years after the onset of epidemic typhus.

Gruber also emphasized the importance of myocarditis in epidemic typhus. Endocarditis was rare. Thromboendocarditis developed on the basis of underlying myocardial infiltration. According to Ash and Spitz, interstitial mononuclear cellular myocarditis is usually present in epi-

virus. Acidophilic intranuclear inclusion bodies are present, but are more homogenous than those observed in yellow fever.

It is assumed that Rift Valley fever is naturally transmitted in sheep and cattle by a mosquito active at night. The existence of a sylvan cycle involving certain mosquitoes and wild animals of unknown species seems probable (Smithburn, Haddow and Lumsden). There is no evidence to suggest that human beings are infected by insect vectors (Dick) and, therefore, they presumably play no part in the survival of the virus (Gledhill). Accidental human infections have been observed in practically every laboratory in which the virus has been studied The infections among persons in close contact with infected animals and carcasses are frequent, but there is no evidence of a person-to-person spread. Infected milk may be a source of the disease

In man the incubation period lasts from five to six days, and the onset of the disease is abrupt with high fever which lasts two to six days. The symptoms are similar to those of influenza, and the temperature is of the saddle-back type. Symptoms and signs referable to liver impairment are absent. The disease lasts for a few days and the convalescent period is short One of the cases recorded by Daubney and Hudson developed defective vision, and early retinal changes have been described (Freed, Shrire). It would appear that the onset of eye symptoms after a febrile illness in Africa should suggest Rift Valley fever as the cause (Dick).

Schwentker and Rivers reported a fatal case of Rift Valley fever in which a laboratory worker died from venous thrombosis 45 days after the onset of the disease. The active stage of Rift Valley fever had subsided some time prior to death.

During the febrile period of the disease a diagnosis can be made by isolating the virus from the patient's blood This may be shown by inoculating mice Acute and convalescent cases can be tested for the existence of virus-neutralizing antibodies, which can still be demonstrated as long as 12 years after recovery (Sabin and Blumberg).

The hepatic lesions produced by Rift Valley fever in animals resemble very much those observed in the liver of humans dying from yellow fever. But there is no reason to assume that Rift Valley fever produces considerable hepatic lesions in man. Congestive and hemorrhagic manifestations, occasionally thrombo-embolic complications, suggest that the chief alterations caused by the disease in man occur in and about blood vessels.

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Tsutsugamushi Disease

According to Settle, Pinkerton and Corbett, generalized vasculitis always occurs in scrub typhus, and it may lead to peripheral collapse. A damaging effect of a rickettsial toxin on peripheral capillaries may also play a role. Myocarditis invariably occurs; viz., in about half the cases it caused myocardial necrosis of varying degree, so that it may have been responsible for death from heart failure. Ash and Spitz regarded interstitial myocarditis as a very striking characteristic of scrub typhus. The myocarditis was characterized by the predominance of large basophilic mononuclear cells, with plasma cells, monocytes and eosinophilic histiocytes also present. The reaction frequently was interfascicular and occurred around the arterioles and venules.

A few myocardial fibers underwent visible degeneration, although fragmentation of myocardial fibers was also common. This disparity between the degree of cellular infiltration and the degeneration of myocardial fibers was pronounced In cases of scrub typhus Sangster and Kay found cardial dilatation and fall of blood pressure on about the twelfth to fourteenth day of severe involvement. Cyanosis was frequently observed, but no heart failure occurred. Howell reported no abnormal electrocardiographic pattern in 200 consecutive cases of patients convalescent from scrub typhus Sokolow and Garland found some electrocardiographic changes in a few convalescents. The cause of cardiovascular impairment in these cases is not thoroughly understood, although it may be attributed to scrub typhus.

Likoff noted electrocardiographic alterations in 10 of 100 patients he observed for seven weeks after scrub typhus. In five of these patients the changes persisted for the entire seven weeks Bundle-branch block occurred in two patients and intraventricular block in one.

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demic typhus. Electrocardiographic alterations observed in epidemic typhus are to be considered not only as sequelae of myocarditis, but also as products of extracordial factors. An abnormal electrocardiogram is not always reliable proof of the presence of myocarditis. A histologically extensive myocarditis may be found in typhus patients with previously normal electrocardiograms, while fatal cases with abnormal electrocardiograms may reveal either a myocarditis or a normal myocardium (Aschenbrenner, Bohn, Norvitt).

Abnormal electrocardiograms during and after epidemic typhus have been reported by Aschenbrenner, Bohn, Cogan and Heinrichsdorf; Cogan, Garreton, Hervé and Solar; Gruebel and Krause; Kuhlmann and Heinrich; Laurentius, Liebau, Norvitt, Robbers; Siedeck, Kasperczik and Fanta; and Yeomans, Snyder, Murray, Ecke, and Zarafonetis. Some authors conclude from electrocardiographic recordings that permanent myocardial impairment in typhus is rare (Gruebel; Siedeck, Kasperczik and Fanta; Robbers).

Schaefer saw chemical changes of the blood and urine in patients suffering from epidemic typhus, and usually found alterations in the chloride content of blood and urine. Altered permeability of the capillaries associated with hypovolemia was also suggested.

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Q Fever

A relative bradycardia, especially in severe cases, is frequent in Q fever. (Dardini; Dennig, Gsell; Gutscher and Nufer, Janton, Bondi and Sigel; Oliphant and Parker; Rilliet and Keil). According to Hengel, Kausche, Laur and Rabenschlag, circulatory collapse is rare, transient electrocardiographic alterations were observed in only one case and patients previously suffering from heart disease had severe cardiovascular involvement. Wendt reported three cases of Q fever associated with myocarditis.

Cervini and Longo described a case of Q fever in which the main feature was a shock-like syndrome. They said that the fall of blood pressure probably resulted from a decreased blood volume and impaired vasomotor activity. In such a shock-like syndrome, intravenous infusions of plasma or plasma substitutes and noradrenaline should be employed. Heni and Germer observed thrombosis and pulmonary embolism, and found there may be pulmonary infarction without demonstrable thrombosis. Disturbances of peripheral vascular circulation with subsequent intermittent claudication also has been seen after Q fever. Such alterations may last 4 to 5 months The convalescent from Q fever may also experience vasolability, inclination to collapse and transient hypertension (Hengel, Kausche, Laur and Rabenschlag)

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